AMERICAN HEART JOURNAL

Volume 55, No. 3
March, 1958

Editorial

The Organization of Vasomotor Control by the Central Nervous System

L. M. N. Bach, Ph.D., New Orleans, La.*

Slowly, and somewhat erratically, our knowledge of the control of vasomotor activity by the central nervous system is expanding. Practically every neurophysiologist tries his hand, at least once, in some problem which concerns the central control of the vascular system. Contributing, in his way, to the somewhat irregular development of this knowledge, he turns or returns to his professional task of prying into the fundamental and fascinating secrets inherent in the intrinsic functional organization of the central nervous system.

Over the past several years a number of neurophysiologists have made singular contributions to the warehouse of facts concerning the influence of the nervous system on the circulation. However, our real understanding of the nature, extent, and significance of these influences must await a fuller comprehension of the manner in which the various regions and levels of the nervous system interact to produce the reflex and behavioral activity so often manifested by circulatory changes. We can only attempt, at this time, to make a brief inventory of some of the significant items in our warehouse of facts.

A number of observations have been made on the pronounced vasomotor effects which result from chemical or electrical stimulation of the cerebral cortex both in man and in lower animals. Unfortunately, the validity of many of these observations is often vitiated because of variations in the types and depths of anesthesia employed. Another limiting factor in interpreting these results is the presence of trigeminal pain afferents in the pia mater, inadvertent stimulation of which may produce reflex vasomotor effects.[1] It is well established, however, that stimulation of the motor areas of the cerebral cortex will produce marked vasomotor responses. The associated changes in blood pressure may range from a marked vasodepressor response in which the blood pressure falls to 50 mm. Hg,[2] all the way to a pronounced hypertensive effect where the blood

*Department of Physiology, Tulane University School of Medicine, New Orleans, La.

pressure rises 110 mm. Hg above the basal level.[3] The direction which these changes in blood pressure may take is complicated by the common observation that stimulation of the motor cortex almost always produces both vasodilatation in skeletal muscle and vasoconstriction in the skin and viscera simultaneously.[2] It is not clear what physiologic processes determine whether hypertensive or vasodepressor effects will prevail.

Although the normal integrated cortical activity which could ordinarily result in pressure changes of these magnitudes is not known, there is some good information about the systems and reflexes brought into play when such effects appear. For one thing, it is known that depressor and pressor points are closely adjacent in the motor cortex so that they presumably are equally accessible to, and even interchangeably activated by, cortical or subcortical fiber relays from other regions.[4] One explanation for the muscular vasodilatation, which appears with vasoconstriction in the skin and viscera, is that a baroceptor reflex compensation occurs for the systemic rise in blood pressure which usually follows stimulation of the motor cortex[5]; this compensation must, peculiarly, produce a specific inhibition of vasoconstrictor fibers to muscle. The vasoconstrictor fibers originating in the motor cortex appear to relay to the cord by at least two different routes. One passes through the hypothalamus and probably relays further through the classical medullary vasomotor centers,[6] ultimately producing generalized and bilateral vasomotor responses.[7] Another vasoconstrictor pathway of major importance descends in the corticospinal tract projection from the motor cortex, decussating at least partially, and generally following the peripheral distribution of the motor nerves.[8] The activation of this pathway can result in localized and unilateral vasomotor changes.

To some extent, muscular vasodilatation is undoubtedly caused by the compensatory reflex inhibition which follows activation of the corticogenic vasoconstrictor systems. However, Uvnäs and his co-workers[9] have recently described what is apparently a much more important vasodilator system, one which originates in the motor cortex and which acts directly on skeletal muscle. This system, terminating in cholinergic fibers which, anatomically, have a sympathetic peripheral distribution, relays in the hypothalamus and midbrain but appears to bypass the medullary vasomotor centers as it descends to the cord.

Our discussion has been limited to just one portion of the cerebral cortex, the "motor" area, classically limited in its function to the provocation of activity of specific motor units of skeletal muscle. There are instances when one has little doubt that the vasomotor effects which originate from this one area alone actually can be as profound as those resulting from any chemical, endocrine, metabolic, drug, traumatic, or reflex influence on the vascular system. Admittedly, the experimental techniques available today have not permitted us to demonstrate unequivocally that such cortically induced effects can result in the sustained, pathologic or fatal characteristics of vascular disease in man. There is at least one striking exception to this general failing, however, which points up the potential influence of the "motor" cortex, at least, in the production of chronic vascular disease. This is the demonstration by Hoff and his associates[10] of the production of intensive and prolonged renal vasoconstriction and the

subsequent induction of ischemic lesions following chronic stimulation of the motor cortex in dogs.

In the author's experience, freshman medical students, who perhaps are the only persons privileged to make the comparison, are frequently astounded by the contrast between the blood pressure effects which they observe in experiments involving manipulation of the circulation in the dog and the effects which they observe later in the same student laboratory when they stimulate the cortex in unanesthetized but curarized cats; often they come away convinced that the cortex is *the* major factor in the control of blood pressure! Against these rather dramatic examples, we must note the extensive and well-controlled observations of Penfield,[11] who finds that in man, under almost ideal conditions of acute cortical stimulation, the cardiovascular responses are, at best, rather moderate.

Of course there are many other areas of the cerebral cortex which have also been found to produce marked vasomotor effects in both man and lower animals. Stimulation of the orbital regions of the frontal cortex can evoke both pressor and depressor effects although the usual physiologic influence of this area appears to be primarily inhibitory to hypothalamic vasoconstrictor mechanisms.[12] The temporal lobes also can provoke pressor and depressor effects, principally by influencing the activity of brainstem or spinal vasoconstrictor elements. This system, in its descent to the cord, avoids the hypothalamic and medullary vasomotor regions[1] and thus appears to be different from any of the previously described tracts. Conjoining this particular system of fibers is a descending tract which originates in the cingulate gyrus, stimulation of which usually results in generalized vasoconstriction.[1,13] Finally, the insula, an important area of the limbic cortex, usually generates vasodepressor effects when stimulated. The course of the descending fibers from this region appears to be similar to that of fibers originating in the orbital areas of the frontal cortex; these likewise project to hypothalamic areas of vasomotor significance.[1]

In contrast to the classical "motor" region of the cortex, the orbital, cingulate, insular, and temporal areas, described above, do not ordinarily initiate skeletal motor responses but seem to have in common the function of establishing those patterns of autonomic and somatic activity which we commonly describe as "emotion." The literal distinction between motion and emotion is the difference between simple movement and "movement outward" (i.e., movement with a "purpose"?). For simple movement, originating in the motor cortex, we find two types of vasomotor control. One is highly and almost exclusively related to vasodilatation in muscle and may be important in exercise. The other is closely, but not solely, correlated with the descending corticospinal tract which represents the major path in the control of the activity of skeletal muscle. Both of these systems could conceivably be concerned with vasomotor changes in emotion but, on the surface, at least, they appear to be primarily concerned with locomotor and simple motor activity. However, the third system from this area, vasoconstrictor in nature and projecting through the classical hypothalamic and medullary pathways, may more likely be involved in emotional reactions. The vasomotor activity evolved from those cortical areas

which are more obviously related to emotional manifestations appears to be more generalized, although the specificity of the responses is not as well worked out as that deriving from the motor cortex. These responses are partly mediated by the classical hypothalamic and medullary vasomotor areas and partly by pathways different from any yet described. We have not given any thought, here, to the variety of interrelationships which have now been established between the motor areas and other regions of the cortex, including those described above. These interrelationships introduce still another order of complexity in the problem of unraveling the principles of cortical control of vasomotor activity. At least, we can conclude that there are a considerable variety of types, origins, courses, and actions among the vasomotor systems originating in the cortex. There are undoubtedly even greater orders of variety of almost completely unknown circumstances in which various combinations of these and as yet undescribed systems can be activated.

Limitations of space preclude any consideration of the considerable number of subcortical processes which influences and controls vasomotor activity and the general status of the vascular system. Merely mentioning some of the outstanding phenomena will perhaps give a brief, but tantalizing, view of the dimensions of the problem area considered in this article. A few salient features of hypothalamic control of vasomotor activity, for example, include the finding that the hypothalamus exhibits a differential control over the secretion of adrenalin and noradrenalin[14]; the observation that simple changes in stimulus parameters at one point in the hypothalamus can reversibly invoke vasodilatation or vasoconstriction[15]; the suggestion that an upset in the autonomic control of glucose metabolism resulting from an imbalance in adrenalin-noradrenalin production[17] may be the basis for the increased fat intake and obesity resulting from hypothalamic lesions,[16] with subsequent implications for the production of atherosclerosis; and the well-substantiated finding that the hypothalamus plays a central role in ACTH production during stress.[18] All of these events contribute inevitably to the difficulty and urgency of interpreting the role of the hypothalamus, particularly, and the central nervous system, generally, in the normal control of vasomotor activity and in the production of vascular disease.

It is too facile to impute a psychogenic origin for all, or even many, of the common vascular diseases despite the strong evidence which implicates the central nervous system in the establishment of patterns of vasomotor responses. By the same token, it would be erroneous to assume that the central nervous system is the dominating factor in the production of vascular disturbances. Nevertheless, it is more than obvious that the central nervous system is as important a link in the chain of events leading to vascular disease as any isolated metabolic, renal or endocrine event. The massive public attention toward and support of research in the cardiovascular diseases deserves the efforts of cardiovascular and neurological investigators alike in developing and sustaining a fruitful interest in the resolution of the problem of the organization of vasomotor control by the central nervous system.

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Hemodynamic Findings at Thoracotomy for Mitral Valve Disease

Max Zoob, M.D., Robert E. Rockney, M.D., and W. P. Cleland, F.R.C.S.*
London, England

Thoracotomy affords a unique opportunity for correlating physiologic and pathologic findings in mitral valve disease. The immediate pressure changes produced by valvotomy have been presented in several previous studies.[1-4] In this paper additional findings in 50 patients with mitral valve disease are presented. Pressure pulses obtained directly from the pulmonary artery and left side of the heart are correlated with the findings of the surgeon (W.P.C.) regarding the valve size and presence or absence of incompetence. The pressure changes produced by valvotomy are correlated with the surgeon's opinion of the increase in valve diameter, and the effect of valvotomy in "pure" mitral stenosis is contrasted with that in mitral stenosis with incompetence. Finally, the relationship between left atrial and pulmonary artery pressure is studied, and the mechanism of the immediate fall of pulmonary artery pressure which sometimes follows valvotomy is discussed.

MATERIAL

The 50 subjects formed a consecutive series of patients submitted to mitral valvotomy in whom adequate pressure pulse records were obtained. Most of the patients had "pure" mitral stenosis (M.S.) but a few were known to have associated mitral incompetence (M.S.I.) of moderate or considerable degree. Since it was realized that the outcome of surgical treatment was uncertain in the latter group, they were submitted to operation only when medical treatment had failed, and it is probable that they had reached a later stage in their natural history than the group with M.S.

Some patients had associated aortic or tricuspid valve disease, but this was relatively slight, and in all cases the mitral valve lesion was the dominant one.

METHODS

After the pericardium had been opened, the left atrium (L.A.), left ventricle (L.V.), and pulmonary artery (P.A.) were punctured with needles of gauge 18 or 22 S.W.G. attached to saline-filled No. 8 cardiac catheters. Pressures were measured with a pair of capacitance mano-

From the Departments of Medicine and Surgery, Postgraduate Medical School of London.
Received for publication Aug. 19, 1957.
*At present, Assistant Professor of Medicine at the University of Colorado School of Medicine, Denver, Colo.

meters whose output was passed to direct current amplifiers and thence to mirror galvanometers. The frequency response of the system was linear to 15 cycles per second. The pressure pulses were recorded photographically, together with a simultaneous electrocardiogram just before the atrium was incised, and again about 10 minutes after it had been closed, when the blood pressure and heart rate had regained a steady state. The recording apparatus was calibrated and zero positions recorded, immediately before and after each set of observations.

In a minority of cases, records were made from atrium and ventricle in quick succession, and the gradient across the mitral valve was estimated from the pressures measured at analogous points of the cardiogram in cycles of equal length. In the majority, L.A. and L.V. pressure were recorded simultaneously from the same base line so that the pressure difference could be measured directly. In all cases the gradient was measured at 3 points of the cardiac cycle: (1) the peak of the A wave, (2) the early diastolic nadir of the ventricular curve, and (3) the R wave of the electrocardiogram (Fig. 1). Theoretically, the first of these probably gives the best estimate of the gradient. In practice, however, the ventricular curve at this point frequently showed an apparent "overshoot," which exaggerated the gradient. This artefact also tended to vitiate planimetric measurements of the mean diastolic gradient, and we have therefore usually preferred to refer to the late diastolic gradient at the R wave of the electrocardiogram. This certainly tended to give a low estimate, but was free of artefact and was applicable to all cases whether in sinus rhythm or atrial fibrillation.

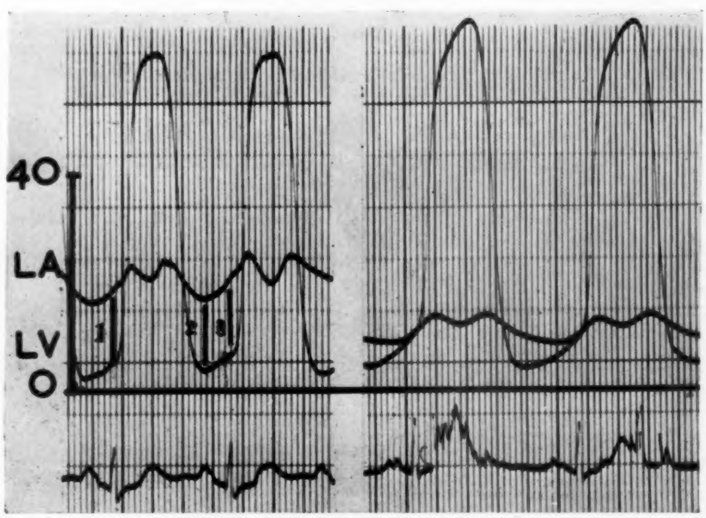

Fig. 1.—Simultaneous left atrial and left ventricular pressure pulses. (*A*, Before valvotomy; *B*, after.) Gradients were measured at three points: (*1*) the peak of the A wave when present, (*2*) the early diastolic nadir of the ventricular curve, and (*3*) the R wave of the electrocardiogram. In practice, (*3*) was found to be the most convenient to refer to since (*1*) was often vitiated by the "overshoot" shown here, and (*2*) was not applicable in atrial fibrillation.

Mean pressures were obtained by tracing the record with its base line on to graph paper of known weight per unit area. The tracing was then cut out and a known length was weighed. The mean height of the curve was then directly calculable and was converted into pressure in the usual way by application of the calibration factor. The valve size and the presence or absence of a regurgitant stream was determined by palpation, both before and after the valve was split. An orifice of 1 cm. diameter or less was described as "severe" stenosis; between 1 and 1.5 cm., as "moderate" stenosis; and over 1.5 cm., as "slight" stenosis. If the operation increased the valve size by 1.5 cm. or more, it was described as a "good split"; if the increase was less than 1.5 cm., it was called a "poor split."

RESULTS

Hemodynamic Findings in Mitral Stenosis Without Incompetence (34 Cases).—The left atrial pressures and mitral valve gradient were highest in the group with severe stenosis, the mean left atrial pressure (L.A.m.) averaging 21.5 mm. Hg as compared with 15.7 mm. Hg in the moderate group. The individual cases are shown in Figs. 2 and 3, and the details of the pressure pulse and gradient are shown in Table I.

The pressure gradient across the mitral valve was greatest in presystole in cases with sinus rhythm, and in early diastole in cases with atrial fibrillation (Table II), due presumably to the fact that the flow is greatest at these times. The gradient reached its lowest value in late diastole at the R wave of the cardiogram when it averaged 13.7 mm. Hg in the severe group and 8.5 mm. Hg in the moderate group. L. A. pressures and gradients were slightly higher in patients with sinus rhythm than in those with auricular fibrillation (Table II).

In the left atrial pulse, the C and V waves were nearly equal in height, averaging 23.8 mm. Hg (11 to 36 mm. Hg) and 24.4 mm. Hg (13 to 40 mm. Hg), respectively, in the severe group, and 17.1 mm. Hg (15 to 34 mm. Hg) and 19.3 mm. Hg

TABLE I. "PURE" MITRAL STENOSIS BEFORE VALVOTOMY

VALVE SIZE	CASES	PULMONARY ARTERY		LEFT ATRIUM							L.A.-L.V. GRADIENT		
		MEAN (MM. Hg)	SYSTOLIC	A	C	V	Y	RY/V	MEAN (MM. Hg)	MEAN DIASTOLIC (MM. Hg)	E.D.	A	R
1 cm. or less	22	40.4	50.1	24.0	23.8	24.4	16.2	0.98	21.5	19.7	13.3	16.4	13.7
1.1 to 1.5 cm. (plus one case with valve 1.8 cm.)	12	22.7	33.5	22.6	17.1	19.3	11.6	1.22	15.7	14.3	6.9	14.9	8.5

The individual cases are shown in Fig. 2.

TABLE II. AVERAGE PRESSURES (MM. Hg) BEFORE VALVOTOMY IN MITRAL STENOSIS WITHOUT INCOMPETENCE

RHYTHM	CASES	SYSTOLIC P.A.	LEFT ATRIUM					L.A.-L.V. GRADIENT	
			C	V	Y	MEAN	MEAN DIASTOLIC	E.D.	R
Sinus	11	50.6	26.6	25.6	17.3	22.3	20.0	12.1	14.[illegible]
Auricular fibrillation	11	50.3	21.1	23.3	15.6	18.2	19.4	13.5	12.[illegible]

Left atrial pressures and gradients are slightly higher in sinus rhythm than in auricular fibrillation.

(1 to 32 mm. Hg), respectively, in the moderate group. There was, however, considerable individual variation, and the V wave was sometimes much taller than C. The average value for V minus C was +1.3 mm. Hg (+8 to −11 mm. Hg). The significance of this in the diagnosis of mitral incompetence is discussed below.

The RY/V ratio averaged 0.98 (0.55 to 1.4) for the severe group, and 1.22 (0.6 to 2.3) for the moderate group. These valves were in the expected range for dynamically significant mitral stenosis.[5]

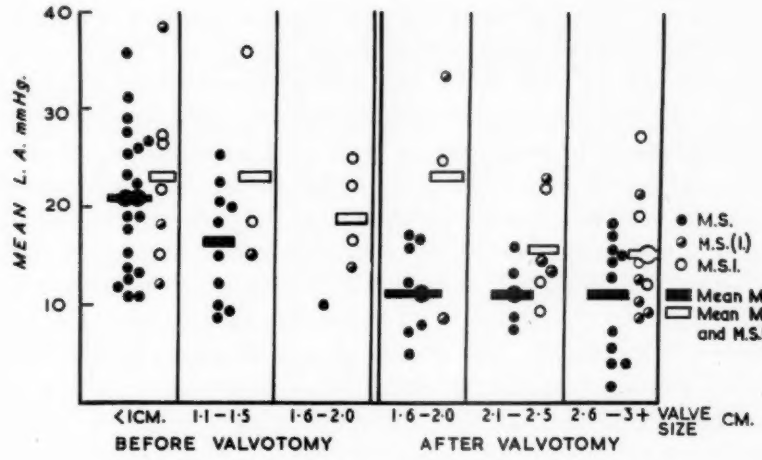

Fig. 2.—The relationship between mean left atrial pressure and valve size. Black circles represent cases of mitral stenosis without incompetence, and the black bars represent the average pressure. Cases of mitral stenosis with moderate or considerable incompetence (M.S.I.) are shown by open circles, and mitral stenosis with slight incompetence [M.S.(I)] by half-open circles. In M.S. the average pressures are highest when the valve size is under 1 cm. diameter, but there is little relation to valve size when this exceeds 1.5 cm. When incompetence is present, pressures are higher and show little relationship to valve size.

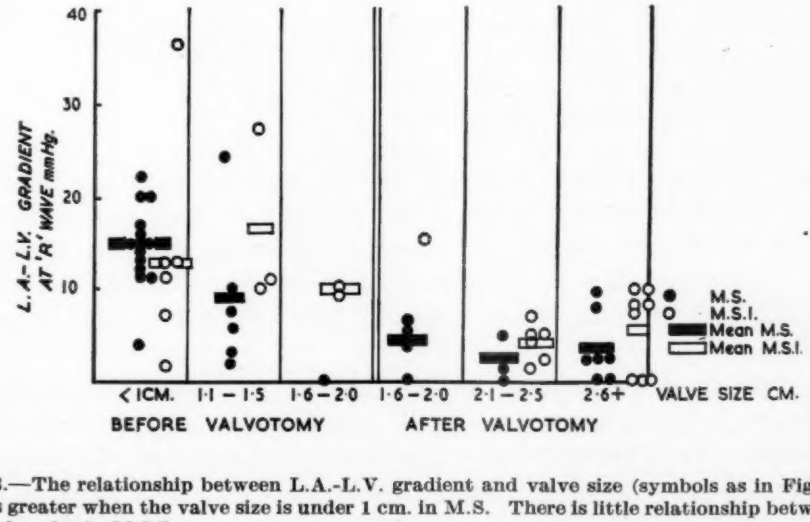

Fig. 3.—The relationship between L.A.-L.V. gradient and valve size (symbols as in Fig. 2). The gradient is greater when the valve size is under 1 cm. in M.S. There is little relationship between gradient and valve size in M.S.I.

The mean pulmonary artery pressure (P.A.m.) averaged 40.4 mm. Hg in the severe group and 22.7 mm. Hg in the moderate group; its relation to the L.A.m. is shown in Fig. 8. In general, it was found that the P.A.m. was raised above normal to a greater extent than the L.A.m., and this disparity was greater the higher the L.A. pressure. In other words, the normal pressure difference between P.A. and L.A. was a little increased in cases in which the L.A.m. was slightly raised, but was grossly exaggerated when the L.A.m. was very high. This is discussed further below.

Effects of Valvotomy in Mitral Stenosis.—

A. *Valve diameter increased by 1.5 cm. or more without production of incompetence:* Pressure measurements were made before and after valvotomy in 11 cases in whom a split of at least 1.5 cm. was achieved without the production of incompetence. The findings in the individual cases are shown in Fig. 5. The L.A.m. fell an average of 12.9 mm. Hg in 8 cases, was virtually unchanged (±5 mm. Hg) in 2, and rose 4 mm. Hg in 1. A fall in the L.A.-L.V. gradient was seen in all 7 cases in which it was measured, the average drop being 10.6 mm. Hg. The fall in L.A.m. was accompanied by a smaller fall in P.A.m. in 7 of 9 cases, the average P.A.m. fall being 6.6 mm. Hg as compared with an average L.A.m. fall of 10.6 mm. Hg. In the remaining 2 cases the changes were too small to be of significance. (In one, the L.A.m. rose 4 mm. with unchanged P.A.m.; in the other, L.A.m. fell 3 mm. while P.A.m. rose 3 mm.) The heart rate was unchanged or slowed in 10 of 11 cases, and the left ventricular systolic (L.V.S.) pressure was unchanged or rose in 6 of the 7 cases in which it was measured, suggesting an increased cardiac output following valvotomy.

TABLE III. "PURE" MITRAL STENOSIS BEFORE AND AFTER SPLIT OF 1.5 CM. OR MORE

	NUMBER	RATE	L.V. SYSTOLIC	P.A. SYSTOLIC	RY/V	GRADIENT AT R	MEAN L.A.
Before	11	76.7 (22.7)	98 (18.6)	41.1 (11.7)	1.05 (0.3)	13.3 (4.7)	20.35 (7.5)
After	11	64.9 (13.5)	102.5 (19.2)	36.5 (12.9)	1.47 (0.6)	0.5 (0.8)	10.64 (5.8)

Figures in parentheses denote standard deviation.

These results are summarized in Table III, from which it will be seen that valvotomy usually reduced the left atrial pressure to near normal levels and brought the RY/V ratio outside the range of critically stenosed valves.[5] The L.A.-L.V. gradient at the end of diastole was practically abolished, but some pressure difference between atrium and ventricle usually remained in early diastole (Fig. 1).

B. *Valve diameter increased by less than 1.5 cm. without the production of incompetence:* Pressure measurements were made before and after valvotomy in 11 such cases. They showed much less improvement in the circulatory state than occurred in the "good split" group just described. The contrast between these groups is shown by Table IV, and the findings in the individual cases by

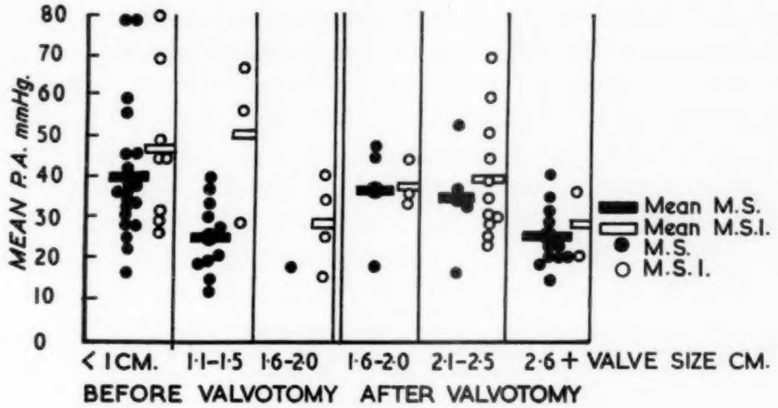

Fig. 4.—The relationship between pulmonary artery pressure and mitral valve size (symbols as in Fig. 2). In M. S. the pressures before valvotomy are related to valve size. This is not so in M.S.I.

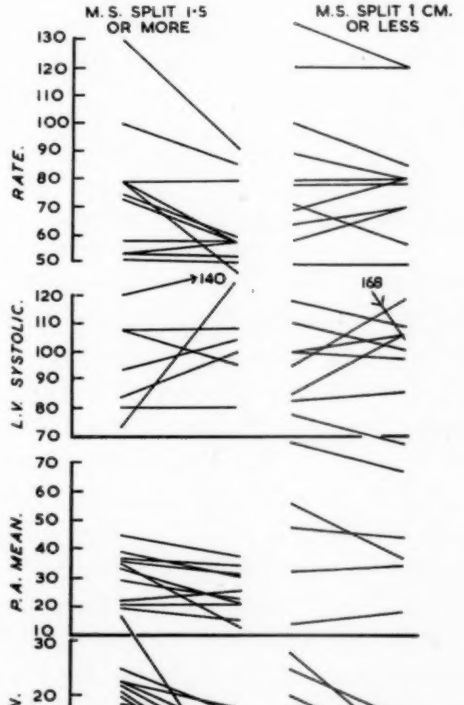

Fig. 5.—The left end of each line represents the initial values, and the right end the final values, of one case. When the valve is split 1.5 cm. or more, irrespective of the initial valve diameter, the left atrial pressure falls considerably. The heart rate usually falls and the systemic pressure is usually unchanged, or rises, suggesting increased cardiac output. When the split is 1 cm. or less, the fall in left atrial pressure is usually smaller, and the left ventricular pressure rises less frequently.

Fig. 5. The L.A.m. fell in only 6 cases (average fall, 10.2 mm. Hg) and was virtually unchanged in the remaining 5. The L.A.-L.V. gradient fell an average of 11.8 mm. Hg in 4 cases, and was virtually unchanged in 3. (It was not measured in the remaining 4.) The heart rate quickened in 3 of 11 cases, and the L.V.S. pressure fell in 4 cases, suggesting a reduction in cardiac output in these patients. The average final pressures were L.A.m. 12.0 mm. Hg (8 to 16.5 mm. Hg), L.A.-L.V. gradient 2.4 mm. Hg (0 to 4 mm. Hg), and RY/V 1.17 (0.7 to 1.9). Thus, the L.A. pressure often remained raised and the RY/V was usually within the range for critically stenosed valves.

TABLE IV. CHANGES IN PRESSURE (MM. Hg) AFTER (A) GOOD SPLIT, (B) POOR SPLIT, AND (C) GOOD SPLIT BUT WITH INCOMPETENCE PRODUCED

GROUP	SPLIT	NUMBER	RATE	L.V. SYSTOLIC	P.A. SYSTOLIC	RY/V	GRADIENT AT R	MEAN L.A.
A	1.5 cm. or more	11	−11.5	+5.8	−4.6 (−14 to +4)	+0.42 (+1.6 to −0.5)	−12.8 (−19 to −6)	−9.7 (−31.4 to +3.8)
B	1 cm. or less	11	0	+1.5	−5.7 (−17 to +7)	+0.21 (+1.3 to −1.1)	−7.1 (−17 to 0)	−6.0 (−16.5 to +0.3)
C	1.5 cm. or more (incompetence produced)	7	0	+9.7	−0.3 (−4 to 14)	+1.3 (+0.5 to +2.9)	−6.0 (+2 to −17)	−3.7 (+1 to −17)

There was no mitral incompetence initially in any of the groups.

C. *Valve diameter increased by 1.5 cm. or more with production of incompetence:* Pressure measurements were made before and after valvotomy in 7 such cases. The changes produced by valvotomy were much less satisfactory than in either of the preceding groups, as can be seen from Table IV. The L.A.m. fell in only 4 cases, the average fall being 8.5 mm., and it rose 1.0 mm. and 11 mm. in the remaining 2 cases in which it was measured. The L.A.-L.V. gradient fell an average of 8.8 mm. Hg in 5 cases, and was unchanged (±2 mm. Hg) in 2. The P.A.m. was virtually unchanged (±5 mm. Hg) in all 7 cases. The heart rate rose 10 per minute in one case, fell 10 per minute in another, and was unchanged in the remainder. The L.V.S. pressure rose an average of 12.6 mm. Hg in 5 cases, fell 5 mm. Hg in one, and was not measured in the remaining case. The average final pressures were L.A.m. 16.7 mm. Hg (11 to 22 mm. Hg); L.A.-L.V. gradient at R, 5.3 mm. Hg (0 to 10 mm. Hg); RY/V 2.5 mm. Hg (1.0 to 4.5 mm. Hg).

In summary, the findings showed that if the valve diameter was increased by 1.5 cm. or more without the production of incompetence, there was almost invariably a pronounced fall in L.A. pressures and gradients, together with evidence of an increased cardiac output. When, however, the valve was split less than 1.5 cm., the L.A. pressures and gradients were unchanged in half the cases, and in several there was evidence suggesting a diminished cardiac output. If

a good split was achieved but incompetence resulted, the results were worse than in either of the previous groups, the L.A.m. falling less and the P.A.m. remaining virtually unchanged.

Hemodynamic Findings in Mitral Stenosis With Incompetence (15 Cases).— When incompetence was present, the initial pressures were much the same whether the stenosis was severe or moderate. This is in contrast to the findings in pure M.S. (Figs. 2, 3, and 4, and Table V). On the other hand, for a given valve size, all pressures were higher in M.S.I. than in M.S. Thus, the P.A.m. averaged 61.5 mm. Hg in M.S.I. as compared with 33.2 mm. Hg in M.S.; L.A.m. averaged 24.5 mm. Hg in M.S.I. as compared with 15.7 mm. Hg in M.S. Four cases with slight incompetence appeared to form an intermediate group with an average P.A.m. pressure of 43 mm. Hg, and L.A.m. pressure of 20 mm. Hg (Fig. 2 and Table VI).

TABLE V. INITIAL PRESSURES (MM. Hg) IN CASES OF MITRAL STENOSIS WITH INCOMPETENCE GROUPED ACCORDING TO VALVE SIZE

GROUP	VALVE	L.A.m.	L.A.-L.V. GRADIENT	P.A.m.
A	< 1 cm.	23.1 (13.1–38.7)	13.2 (2.0–36.2)	46.2 (26–78)
B	1–1.5 cm.	23.1 (15.0–35.5)	16.1 (10.1, 11.0, and 27.2)	49.1 (27, 55, and 65)
C	Over 1.5 cm.	19.9 (15.5–25.0)	10.0	28.3 (15–40)

The pressures are much the same whether the stenosis is (A) severe or (B) moderate. This is in contrast to the findings in pure mitral stenosis (Figs. 1, 2, and 3).

TABLE VI. THE AVERAGE PRESSURES IN MITRAL STENOSIS WITH CONSIDERABLE INCOMPETENCE (M.S.I.), IN MITRAL STENOSIS WITHOUT INCOMPETENCE (M.S.), AND IN MITRAL STENOSIS WITH SLIGHT INCOMPETENCE [M.S.(I.)]

LESION	NUMBER	SYSTOLIC P.A.	C	V	Y	MEAN L.A.	GRADIENT R
M.S.	12	33.2 (±12.8)	17.1 (±8.9)	19.3 (±8.6)	11.6 (±5.0)	15.7 (±6.4)	8.5 (± .7)
M.S.(I.)	4	43.7 (±20.1)	22.3 (±9.2)	26.6 (±13)	15.2 (±5.1)	20.5 (±9.1)	9.3 (±5.9)
M.S.I.	11	61.5 (±28.3)	27.1 (±7.1)	30.9 (±8.3)	19.1 (±7.4)	24.5 (±7.4)	13.5 (±10.3)

The Left Atrial Pressure Pulse Contour.—The significance of the pulmonary capillary, or left atrial pressure pulse contour, in the diagnosis of mitral incompetence has been studied by other workers who have usually concluded that, although a very tall V wave is suggestive of incompetence, it does not necessarily indicate its degree, and is sometimes seen in mitral stenosis without incompetence.[6-11] Our findings are in agreement with these conclusions. The average difference between C and V was much the same whether incompetence was present or not (Table VI). Moreover, of 11 patients with considerable incompetence, V

exceeded C by more than 3 mm. in only 3 cases in whom the values for V minus C were 4,11, and 9 mm. Hg. On the other hand, in 5 cases with M.S., V exceeded C by 4, 5, 7, 7, and 8 mm. Hg. It follows that V wave exceeding C by 10 mm. Hg or more is suggestive of incompetence but is uncommon; a small V wave does not exclude the presence of considerable incompetence.

When reflux was produced or increased at operation, the value for V minus C increased in 5 cases and diminished in 2. Conversely, in 8 cases in which the value for V minus C increased, the production of incompetence had been noted in 5. Thus, an observed increase in the height of V is a suggestive though fallible sign of the production of incompetence.

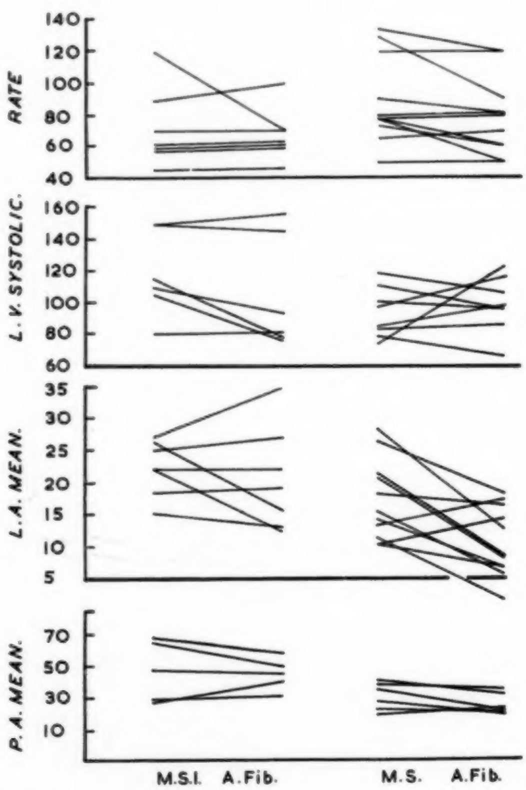

Fig. 6.—The effects of valvotomy in mitral stenosis with incompetence (*M.S.I.*) contrasted with a matched group of cases with pure mitral stenosis (*M.S.*). (Symbols as in Fig. 4.) Note that in most of the cases of M.S.I. the left atrial pressure failed to fall and the systemic pressure failed to rise. In M.S. the left atrial pressure usually fell considerably and systemic pressure rose in several cases.

The Effects of Valvotomy in Mitral Stenosis With Incompetence.—Pressure measurements were made before and after valvotomy in 10 such patients. Only 5 of them showed improvement comparable with that seen in pure mitral stenosis, the L.A.m. falling an average of 12.4 mm. Hg (7 to 23 mm. Hg); the L.A.m. in the remainder was virtually unchanged (±5 mm. Hg) in 4 cases and rose 8 mm. Hg in 1 case.

The L.A.-L.V. gradient fell in 3 cases (8, 13, and 30 mm. Hg), was virtually unchanged in 6 cases, and rose 7 mm. Hg in 1 case.

The P.A.m. fell an average of 15.2 mm. Hg in 4 cases (10 to 26 mm. Hg), was virtually unchanged in 3, rose 11 mm. Hg in 1, and was not measured in the remaining 2 cases.

The L.V.S. pressure rose an average of 14.0 mm. Hg in 4 cases (8 to 18 mm. Hg), was virtually unchanged in 3, and fell in 3 cases (18, 30, and 38 mm. Hg). The heart rate was unchanged in 6 cases, slowed in 2 cases (by 40 or 50 per minute), and quickened in 2 cases (by 10 and 50 per minute).

In summary, the findings suggest that valvotomy produced improvement in only about half the cases in this group. The changes contrast sharply with those in a matched group of cases of pure mitral stenosis, atrial fibrillation, and similar valve size. A good split was obtained in only 3 of 11 cases of M.S. as compared with 5 of 7 cases of M.S.I. Nevertheless, the L.A.m. fell appreciably in 7 of the M.S. cases but in only 2 of the M.S.I. group. The average change was −6.2 mm. Hg in M.S. compared with −1.7 mm. Hg in M.S.I. The L.V.S. pressure rose in 4 of 8 cases of M.S., but in only 2 of 6 cases of M.S.I. The average change was +3.5 mm. Hg in M.S., and −11.9 mm. Hg in M.S.I. (Fig. 6 and Table VII).

TABLE VII. THE CHANGES (IN MM. Hg) PRODUCED BY VALVOTOMY IN MITRAL STENOSIS WITH CONSIDERABLE INCOMPETENCE AND IN PURE MITRAL STENOSIS WITH VALVES OF COMPARABLE SIZE

LESION	GOOD SPLIT	POOR SPLIT	TOTAL	CHANGES				
				RATE	L.V. SYSTOLIC	P.A. SYSTOLIC	GRADIENT	L.A. MEAN
M.S.I., A.F.	5	2	7	−5.7	−11.9	−2.0	−1.5	−1.7
M.S., A.F.	3	8	11	−8.0	+3.5	−3.0	−6.7	−6.2

Despite an anatomically good split, cases of M.S.I. showed slighter falls in L.A. pressures and gradient than cases of M.S.

The Effect of Valvotomy on the Pulmonary Artery Mean Pressure.—The behavior of the P.A.m. immediately after valvotomy might be expected to throw some light on the mechanism of pulmonary hypertension in mitral valve disease. Pressures before and after valvotomy were obtained in 29 cases in whom the valve diameter was increased by 1 to 3 cm. The change in P.A.m. in relation to change in L.A.m. is shown in Fig. 7. It will be seen that there is little correlation between the two, whether the patients with M.S.I. are considered separately or not. Of the many other factors which may be involved in the relationship, the cardiac output is probably the most important and the cases are therefore considered in subgroups taking the left ventricular systolic pressure into account.

A. *P.A.m. and L.A.m. unchanged; L.V.S. usually unchanged:* There were 8 cases in this group which requires no comment since P.A.m. would not be expected to change if L.A.m. was unaltered.

B. *P.A.m. fell; L.A.m. usually fell; L.V.S. fell:* The fall in cardiac output might well have been responsible for the fall in P.A.m. in the 5 cases in this group.

C. *P.A.m. unchanged (±5 mm. Hg); L.A.m. fell; L.V.S. rose:* In 7 cases P.A.m. fell an average of only 1 mm. Hg despite a fall of L.A.m. averaging 12.3 mm. Hg (6 to 19 mm. Hg). The L.V.S. rise averaged 21.5 mm. Hg, so that an increased cardiac output may have prevented the expected fall in P.A.m. The initial P.A.m. in this group was relatively low, averaging 35.2 mm. Hg (22 to 44 mm. Hg).

D. *P.A.m. fell; L.A.m. fell; L.V.S. usually unchanged or rose:* In 8 cases there was a fall in P.A.m. averaging 11.9 mm. Hg (9 to 26 mm.), together with a fall of L.A.m. averaging 10.5 mm. Hg (+1 to −23) with an unchanged or increased L.V.S. pressure. In all but 1 of these cases the changes in P.A.m. and L.A.m. were within 4 mm. of each other. The average initial P.A.m. in this group was 48.9 mm. Hg (19 to 78 mm.).

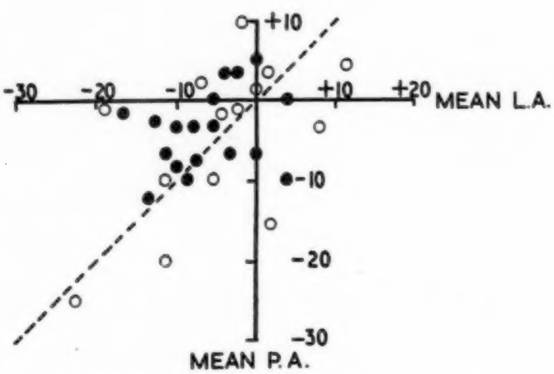

Fig. 7.—The change in mean left atrial pressure following valvotomy is plotted against the change in mean pulmonary artery pressure in mm. Hg, the dotted line indicating a 1:1 relationship. Open circles denote cases of mitral stenosis with incompetence. It is seen that there is no direct relationship between the change of P.A. and L.A. pressures.

In summary, therefore, if valvotomy increased the systemic pressure and lowered the left atrial pressure, the pulmonary pressure fell equally if it was initially over 40 mm. Hg, but remained virtually unaltered if it was initially under 40 mm. Hg.

DISCUSSION

In our observations the heart rate was usually slower and pressures lower than those found on cardiac catheterization, during which it is often difficult to secure truly basal conditions. By contrast, the metabolism of patients anesthetized with nitrous oxide and Pethidine (meperidine hydrochloride) together with muscle relaxants and oxygen is probably very low and steady.[13] Thoracotomy may possibly reduce the total cardiac output by abolishing the negative intrathoracic pressure which normally assists the venous return. It is unlikely, however, to alter materially the relationship between the pressures in the various cardiac chambers and great vessels. It seems justifiable, therefore, to assume that the findings at thoracotomy represent the hemodynamics of mitral stenosis quite faithfully but at lower levels of pressure and output than those usually encountered at cardiac catheterization.

Our findings were, in general, similar to those of previous workers.[1-4] Various additional facts, however, came to light during the present study. In pure mitral stenosis the average left atrial pressures and gradients were highest in the group with the smallest valves, whereas in cases with associated incompetence there was no relationship between left atrial pressure and valve size (Fig. 2). This is presumably because in mitral incompetence the left atrial pressure is determined to a considerable extent by the volume of reflux. Similarly, the prevalvotomy pulmonary artery pressure appeared to be inversely related to valve size in pure mitral stenosis, but the relationship was less clear when there was associated incompetence (Fig. 4). Table VI shows that for a given valve size the average pulmonary artery and left atrial pressures are much higher in the group with moderate or considerable incompetence than in pure mitral stenosis, cases with slight incompetence appearing to form an intermediate group. These findings might represent the added effect of incompetence on the circulation, but they might be due simply to the fact that the group with associated incompetence had reached a later stage in their natural history before being submitted to surgical treatment.

Our findings, like those of previous workers,[6-11] show that a tall V wave in the L.A. pulse is of limited value in the diagnosis of incompetence, for it was often absent in M.S.I. and present in M.S. If, however, the V was conspicuously increased following valvotomy, it usually meant that incompetence had been produced. The pressure changes following valvotomy correlated well with the surgeon's opinion of the size of the split obtained, and the presence or absence of incompetence. Following a good split without the production of incompetence there was a marked fall of L.A. pressures and gradients and a probable increase of cardiac output. When a poor split was obtained, the L.A pressures fell in fewer cases and to a less extent. Results were worse still in cases in whom incompetence had been produced. They were also poor in cases who had incompetence from the outset. In these, even though a good split was obtained, the L.A.m. remained unchanged or rose in half the cases, and there was sometimes evidence suggesting a fall in cardiac output.

It is noteworthy that even in the best cases, namely, patients with pure mitral stenosis in whom a good split was achieved, the L.A. pressures did not usually fall to completely normal levels. The L.A.-L.V. gradient might be abolished at the end of diastole, but a pressure difference usually remained in early diastole or during atrial contraction. This finding is consistent with the clinical observation that the physical signs of mitral stenosis are diminished but not abolished by valvotomy.

The relationship between the P.A.m. and L.A.m. is of considerable interest because neither the mechanism of pulmonary hypertension nor its behavior following valvotomy is completely understood. In Fig. 8 are seen the before valvotomy values for L.A.m. and P.A.m. pressure plotted against one another. If these cases are considered to form a continuous series, it will be seen that the P.A.m. rises disproportionately to the L.A.m. This is so, even at low levels of L.A.m. pressure, when a 10 mm. Hg rise of L.A.m. produces a rise of about 15 mm. Hg of P.A.m. At higher levels of L.A.m. the disproportion is still greater.

This suggests that there was an increase in the pulmonary vascular resistance in all the cases, but that it was greatest in those with the highest left atrial pressures.

The P.A.m./L.A.m. relationship immediately following valvotomy might be expected to indicate whether this increased resistance was due to a reversible vasoconstriction or not. In fact, a disproportionate fall in P.A. pressure was not

Fig. 8.—Mean pulmonary artery pressure and mean left atrial pressure in mm. Hg for all cases before valvotomy. The cases appear to form a continuous series in which for every 10 mm. Hg of L.A. pressure there is a rise of about 15 mm. Hg of P.A. pressure.

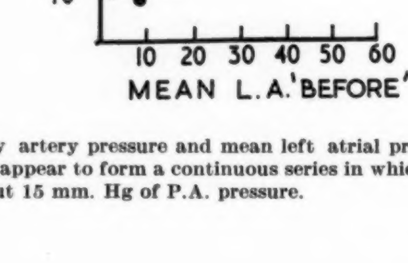

Fig. 9.—Mean pulmonary artery pressure and mean atrial pressure in mm. Hg for all cases after valvotomy. The cases appear to form a continuous series in which for every 10 mm. Hg rise of L.A. pressure there is a rise of about 15 mm. Hg of P.A. pressure.

observed apart from 5 cases in which there was probably a serious fall in cardiac output. In the remainder, the P.A.m. and L.A.m. fell equally, if the initial L.A.m. was high. If the initial L.A.m. was low, the P.A.m. fall was only about half that of the L.A.m. fall. This relationship is similar to that found by Lasser and Loewe[12] in acute experiments in dogs, and it would seem that the immediate

fall of P.A.m. pressure following valvotomy is a purely passive result of lowering the L.A.m. pressure. Some confirmation of this can be obtained by plotting the after values for P.A.m. against the L.A.m. (Fig. 9). If the cases are again considered to form a continuous series, it will be seen that there is still a disproportionate rise of P.A.m. for a given rise of L.A.m. We are, therefore, in agreement with Ellis and his associates[3] in concluding that no immediate reduction in pulmonary vascular resistance occurs at valvotomy, and that the immediate fall of P.A. pressure, which is sometimes seen, is a passive effect of the reduction in L.A. pressure.

SUMMARY AND CONCLUSIONS

Pressure pulses have been recorded by puncture of the left heart and pulmonary artery at thoracotomy in 50 patients with mitral valve disease. Observations were repeated about 10 minutes after valvotomy when the circulation had regained a steady state.

In pure mitral stenosis, initial pulmonary artery and left atrial pressures were inversely related to the size of the valve, the smallest valves being associated with the highest pressures. When incompetence was present, the pulmonary artery and left atrial pressures appeared to be related to its degree rather than to the size of the valve. The initial height of the V wave in the left atrial pulse was an unreliable guide to the presence of incompetence, but an observed increase in height following valvotomy suggested that incompetence had been produced.

If in pure M.S. the valve was split 1.5 cm. or more, there was a conspicuous fall in left atrial pressure usually associated with a rise in left ventricular systolic pressure and fall in heart rate, suggesting an increased cardiac output. The gradient across the mitral valve was markedly diminished but not abolished. If a split of only 1 cm. or less was achieved, the fall in left atrial pressure and gradient was slighter and there was little change in rate or in left ventricular systolic pressure. When incompetence was produced, the fall in L.A. pressure was less than in either of the previous two groups.

In cases with mitral stenosis and incompetence, valvotomy reduced the left atrial pressure in only half the cases. In the remainder it was unchanged or rose, and in some there appeared to be a fall in cardiac output.

The effect of valvotomy on the pulmonary artery pressure was variable. A substantial reduction of a high initial left atrial pressure was usually accompanied by a nearly equal reduction of the pulmonary artery pressure, together with signs of increased cardiac output; when the initial left atrial pressure was lower, the fall in pulmonary artery pressure was only about half the fall in left atrial pressure. These findings suggest that the fall in pulmonary artery pressure is a passive effect and that there is no immediate diminution of pulmonary vascular resistance following valvotomy.

We are grateful to Professor J. McMichael and Dr. J. F. Goodwin for their helpful criticism and advice, and to J. Robson and A. Ager for technical assistance.

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Congenital Mitral Stenosis Associated With Coarctation of Aorta, Bicuspid Aortic Valve, Hypoplasia of the Left Ventricle, Mitral Stenosis, Auricular Septal Defect, and Tricuspid Valvular Malformation

Colin A. Munroe, M.D., George E. Maha, M.D.,** and Edward S. Orgain, M.D.*
Durham, N. C.

Congenital heart disease presenting multiple malformations is not uncommon. The exhibition of the following 6 defects, namely, mitral stenosis, hypoplasia of the left ventricle, bicuspid aortic valve, coarctation of the aorta, atrial septal defect, and malformation of the tricuspid valve, is most unusual. This patient presented an interesting and difficult problem from the diagnostic standpoint. Although an accurate clinical diagnosis was not made until autopsy, the major defects were suspected from a logical analysis of the clinical findings.

CASE REPORT

This 1-month-old white male infant was referred to Duke Hospital because of a heart murmur and cardiac enlargement. The child had been considered normal at birth, but at 2 weeks of age became irritable and developed a nonproductive cough with rapid breathing.

First Admission (*April 16 to 23, 1954*).—On admission to the hospital, irritability, cough, and rapid respirations were observed. There was no cyanosis or clubbing. The heart was greatly enlarged to percussion. A Grade 3 systolic murmur was heard over the entire precordium, and a pulsating liver was palpable below the right costal margin. Pulsations were absent in the lower extremities. The blood pressure was 170/120 mm. Hg in both arms, and 75 mm. Hg in the lower extremities by the Flush method. The electrocardiogram exhibited right axis deviation and right ventricular hypertrophy as shown in Fig. 1,*A*. Fluoroscopy and roentgenograms of the chest revealed marked cardiac enlargement, predominantly right ventricular, and increased pulmonary vascular markings (Fig. 2). Routine blood and urine examinations were normal. Clinical diagnoses of coarctation of the aorta and of patent ductus arteriosus entering proximal to the site of the coarctation were made. It was thought advisable to delay operation, if possible, until the child was 4 or 5 years of age. Following routine care and digitalization, great improvement was effected.

After discharge from the hospital, improvement continued, and at the age of 13 months the child began to walk. However, about 1 year after the first hospitalization, his parents reported

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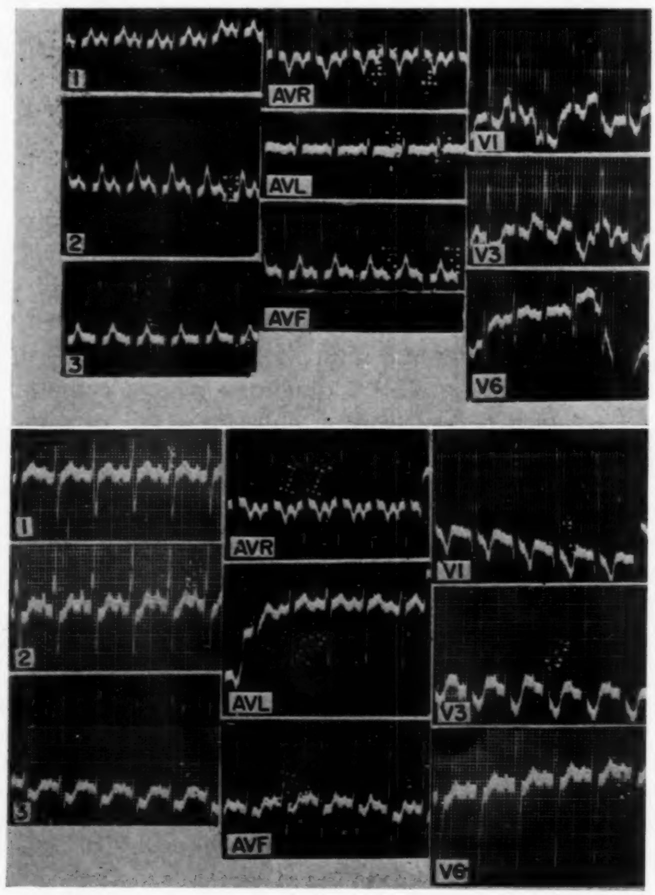
From the Department of Medicine, Duke University School of Medicine, and the Cardiovascular Service, Duke Hospital, Durham, N. C.
Received for publication Aug. 19, 1957.
*Formerly, National Heart Trainee, National Heart Institute, United States Public Health Service, 1955-57. Present address: Hollywood, Fla.
**National Heart Trainee, National Heart Institute, United States Public Health Service, 1956-57.

the occurrence of periodic episodes of dyspnea, respiratory distress, tachycardia, and profuse sweating. In spite of sodium restriction and digitalis, his condition deteriorated and hospitalization again proved necessary.

Second Admission (*Nov. 7 to 22, 1955*).—On the second admission, at 19 months of age, duskiness of the face without blueness of the legs was noted. Blood pressure in the arms was 190/100 mm. Hg, but no pulse or blood pressure in the legs was obtainable. A booming first heart sound was heard with a to-and-fro murmur over the lower central precordium. Fluoroscopy and roentgenograms of the chest revealed the heart and pulmonary arteries to be greatly enlarged, with heavy pulmonary vascular markings. No auricular enlargement was noted. The electrocardiogram again suggested right ventricular hypertrophy.

A.



B.

Fig. 1.—*A*, Electrocardiogram at 2 months of age; *B*, at 23 months of age.

An additional diagnosis of atrial or ventricular septal defect was considered, but the patient was thought to be too young for cardiac catheterization at this time. In view of his general deterioration it was felt that repair of the coarctation might be beneficial, as it would reduce to some extent the left-to-right shunt through the patent ductus. At operation a coarctation 4 mm. in diameter was found below the junction of the left subclavian artery in the transverse arch. The ductus arteriosus was not patent, but the remnant was surgically excised. Pulmonary artery pressure measured intra-arterially at operation was 120/60 mm. Hg as compared to the peripheral arterial pressure of 150/65 mm. Hg. An atrial or ventricular septal defect was

suspected because of the marked right ventricular hypertrophy and pulmonary vascular changes. The coarctation of the aorta was corrected by excision of the narrowed segment and an end-to-end anastomosis. Further surgery at this time was not deemed safe in view of the child's poor condition.

On the second postoperative day the blood pressure was 200/170 mm. Hg in the lower extremities as compared with 170/110 mm. Hg in both arms. On the seventh postoperative day the blood pressure in the legs had dropped to 180/110 mm. Hg, and in the arms to 150/100 mm. Hg. His color and general condition appeared improved, and he was discharged on digitalis and restricted activity.

Ten days after operation the patient returned to Duke Hospital because of repeated episodes of dyspnea with orthopnea, sweating, tachycardia, anorexia, weight loss, and marked weakness.

Third Admission (Dec. 2 to 11, 1955).—On the third admission, at 21 months of age, the child was thin and irritable but not visibly cyanotic. A harsh systolic murmur was heard over the entire precordium, loudest along the left sternal border. The liver was palpable 4 cm. below the right costal margin, but the spleen was not felt. Good pulses were noted in the lower extremities. Blood pressure in the arms was 150/70 mm. Hg, and in the legs 125/? mm. Hg. The electrocardiogram suggested further right ventricular hypertrophy (Fig. 1,*B*). Fluoroscopy and roentgenograms demonstrated tremendous cardiac enlargement, predominantly right sided, and increased vascularity of the lungs with pulsation of the hilar vessels (Fig. 3).

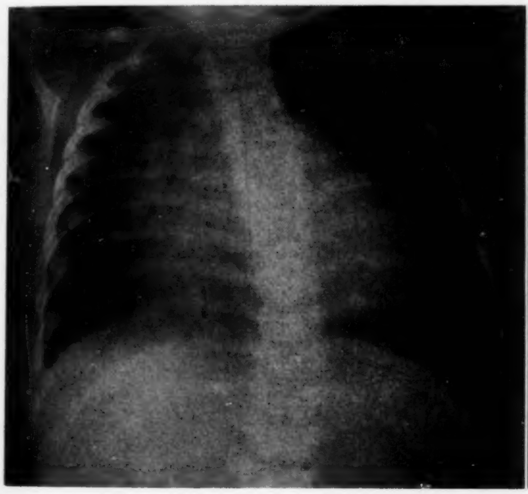


Fig. 2.

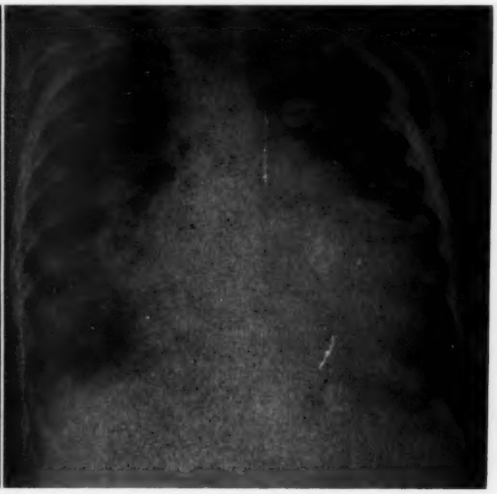


Fig. 3.

Fig. 2.—Initial x-ray of chest which revealed cardiomegaly and increased pulmonary vascular markings.

Fig. 3.—X-ray, taken 18 months after Fig. 2, revealed further cardiomegaly and prominence of pulmonary vascular markings.

During this hospital stay the child improved although mild nocturnal episodes consisting of irritability, sweating, dyspnea, pallor, and tachycardia of 130 to 140 beats per minute were observed. These attacks responded well to placing the child in the upright position. He was discharged on digitalis and restricted activity.

Fourth Admission (Feb. 19 to 26, 1956).—Approximately 2 months after the previous admission, at the age of 23 months, the patient entered Duke Hospital for the final time, because of dyspnea and the initial appearance of peripheral edema. Examination again disclosed a thin, irritable, acyanotic, crying infant with marked dyspnea, and edematous feet and ankles. Blood pressure in the arms was 110/75 mm. Hg, but the blood pressure in the legs was not recorded. There was a loud, harsh, systolic murmur heard over the entire precordium, and a Grade 3 diastolic murmur at the apex. The lungs exhibited râles bilaterally and the liver was enlarged

and pulsating 6 cm. below the right costal margin. In spite of treatment the patient showed progressive tachypnea, tachycardia, orthopnea, pulmonary and peripheral edema, and increasing hepatomegaly. Expiration occurred 7 days after admission.

Gross post-mortem examination revealed the repaired coarctation of the aorta, congenital mitral stenosis, an atrial septal defect, hypoplasia of the left ventricle and aorta, a bicuspid aortic valve, unclassified nonstenotic malformation of the tricuspid valve, marked right auricular and and right ventricular dilatation and hypertrophy, severe pulmonary arteriosclerosis, bilateral pulmonary edema, and visceral congestion. The right ventricular wall measured 1 cm. in thickness while the left measured 4 mm. In the atrial septum there was a defect measuring 1 by 3 cm. and thought to be in the area of the foramen ovale. The mitral valve was stenotic as a result of hypoplasia with shortening of the chordae tendineae and tying down of the valve margins. The valve was slitlike in shape, measured 9 mm. in length, and when forced open was 2 mm. in width. A lesser degree of involvement of the tricuspid valve was seen, with rolled margins and only focal anchoring by shortened chordae. The aortic valve revealed one normal cusp, with fusion of the other two cusps forming a bicuspid valve. Fig. 4 shows a diagrammatic representation of the multiple congenital cardiovascular defects.

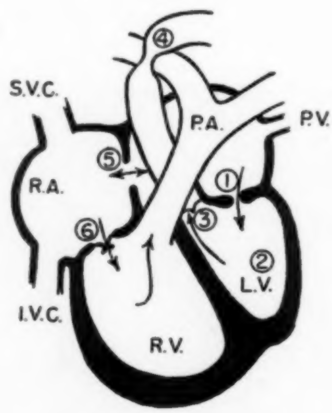


Fig. 4.—Diagrammatic representation of the multiple congenital cardiovascular defects. *1*, Mitral stenosis. *2*, Hypoplasia of left ventricle. *3*, Bicuspid aortic valve. *4*, Repair of coarctation, adult type. *5*, Atrial septal defect. *6*, Malformation of tricuspid valve.

On microscopic examination there was no evidence of rheumatic involvement. The coronary vessels were free of sclerosis. The lungs demonstrated striking pulmonary vascular sclerosis with intimal fibrosis, medial hypertrophy, and elastic fragmentation. Many vessels were occluded by fibrotic proliferation in the subintimal tissues. The veins were also noted to be thick walled, resembling visceral arterioles.

DISCUSSION

The diagnosis of coarctation of the aorta was obvious because of the difference in blood pressure in the upper and lower extremities. It was proved at operation and surgically removed. Patent ductus arteriosus was originally suspected because of evidence of increased flow to the lungs, and the to-and-fro murmur heard over the lower central precordial area. At the time of excision of the coarctation of the aorta a remnant of the ductus arteriosus was removed, but on pathologic examination no patency could be demonstrated. In the absence of patent ductus arteriosus, the marked right ventricular enlargement, the increased blood flow to the lungs with hilar pulsations, and the electrocardiographic

evidence for right ventricular hypertrophy suggested the diagnosis of an atrial septal defect. The absence of electrocardiographic or roentgenologic signs of left ventricular hypertrophy virtually excluded the diagnosis of a sizeable ventricular septal defect. The mitral diastolic murmur, the recurrent bouts of pulmonary edema, and rapid deterioration of the child's condition all suggested the additional diagnosis of congenital mitral stenosis.

There were no clinical or laboratory findings to suggest the presence of a bicuspid aortic valve or a congenital tricuspid defect. However, the frequency with which one finds a bicuspid aortic valve in the presence of coarctation of the aorta is well known.[1]

Ferencz and associates[2] have stressed the importance of the consideration of congenital mitral stenosis in patients with pulmonary hypertension and pulmonary edema in the presence of an atypical clinical picture of patent ductus arteriosus or coarctation of the aorta associated with a disproportionate degree of right ventricular hypertrophy. They collected 34 cases of congenital mitral stenosis reported in the literature between 1946 and 1954, and added 9 cases of their own. Congenital mitral atresia, nonfunctioning left ventricle, and Lutembacher's syndrome were not included. Since their review, 5 other cases have been reported,[3-6] making a total of approximately 48 cases prior to our own. Of the 43 cases reported by Ferencz,[2] only 8 showed isolated mitral stenosis, while the remainder had such associated lesions as aortic stenosis, coarctation of the aorta, and patent ductus arteriosus. No instance of congenital mitral stenosis associated with significant defect of the atrial septum was observed. Our patient exhibited this combination, thus supporting the contention that Lutembacher's syndrome can be congenital in origin as well as acquired.

In the past, several theories have been advanced as to the cause of congenital mitral stenosis. The old theory of "fetal endocarditis" has now been practically abandoned. The frequency of association of endocardial fibroelastosis and isolated mitral stenosis has influenced many to believe that fibroelastosis is responsible for the valvular deformity.[4,5,7] However, in the case presented here fibroelastosis was absent, and multiple defects were present. An explanation for the existence of mitral valve deformity with multiple cardiac defects was offered in the last century by Rokitansky as quoted by Maude Abbott.[8] It was suggested that an abnormal and disproportionate division of the A-V canal and great vessels could result in aortic defects associated with left-sided heart deformities. The frequent association of mitral stenosis complicating congenital aortic deformities, as noted in this case and in those described by Ferencz, make this explanation a plausible one.

SUMMARY

A case of congenital mitral stenosis associated with coarctation of the aorta, bicuspid aortic valve, atrial septal defect, hypoplasia of the left ventricle, malformation of the tricuspid valve, marked right auricular and right ventricular dilatation and hypertrophy, bilateral pulmonary artery sclerosis and pulmonary congestion is presented. The literature concerning congenital mitral stenosis with and without combined defects is reviewed and theories as to the etiology

are discussed. The importance of a careful analysis of the clinical, electrocardiographic, fluoroscopic, and x-ray findings for precise diagnosis of multiple congenital lesions is stressed.

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An Aid in Calculation of Orifice Area of Stenotic Mitral and Aortic Valves

Ralph J. Slonim, M.S., M.D., and Harry Goldberg, M.D.,** Philadelphia, Pa.*

Formulae for the calculation of the area of orifice of stenotic cardiac valves have been described. A graphic method is herein presented whereby calculation of mitral and aortic valve area by these formulae is simplified.

The rate of flow of a fluid across an orifice depends, among other considerations, upon the area of the orifice and the difference in pressure across the orifice. Gorlin and Gorlin[1] have derived, on theoretical grounds, mathematical expressions for flow through cardiac valves and defects. With these, they were able to provide formulae by which the effective orifice areas might be calculated. Using pulmonary artery wedge pressure as an index of left atrial pressure, and assuming a left ventricular mean diastolic pressure of 5 mm. Hg, they found that their calculated areas for mitral valves agreed quite closely with valve areas measured at surgery or autopsy. They did not catheterize the left heart and, therefore, did not attempt to calculate aortic valve area, although they discussed a formula for aortic valve area.

The formulae are not applicable in the presence of regurgitation or an intracardiac shunt, or in the absence of a pressure gradient across the valve to be measured.

The formulae are as follows:

$$\text{M.V.A.} = \frac{\text{M.V.F.}}{31\ \sqrt{\text{V.F.G.}}} \qquad \text{A.V.A.} = \frac{\text{A.V.F.}}{44.5\ \sqrt{\text{S.P.G.}}}$$

$$\text{M.V.F.} = \frac{\text{C.O.} \times 1{,}000}{\text{V.F.P.}} \qquad \text{A.V.F.} = \frac{\text{C.O.} \times 1{,}000}{\text{S.E.P.}}$$

$$\text{V.F.P.} = \text{D} \times \text{H.R.} \qquad \text{S.E.P.} = \text{S} \times \text{H.R.}$$

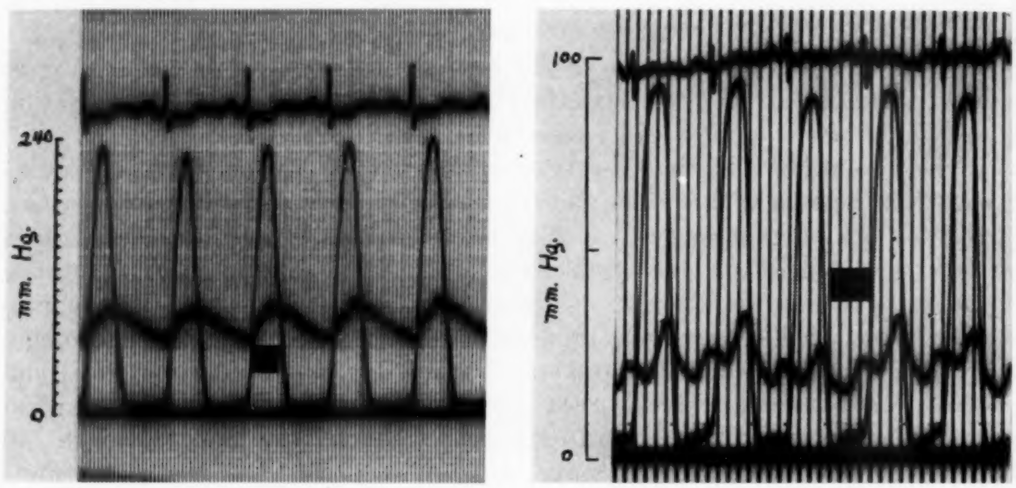
From the Brith Sholom Cardiopulmonary Laboratory, Hahnemann Medical College and Hospital of Philadelphia, and Bailey Thoracic Clinic, Philadelphia, Pa.

Received for publication Aug. 21, 1957.

*Fellow in Cardiology, Department of Medicine and Brith Sholom Cardiopulmonary Laboratory, Hahnemann Medical College and Hospital of Philadelphia, Philadelphia, Pa. This work was done during the tenure of a National Heart Institute Traineeship.

**Assistant Professor of Medicine, Hahnemann Medical College and Hospital of Philadelphia; Director, Brith Sholom Cardiopulmonary Laboratory, Hahnemann Medical College and Hospital of Philadelphia; and Cardiologist, Bailey Thoracic Clinic, Philadelphia, Pa.

M.V.A. and A.V.A.—mitral and aortic valve areas in square centimeters.
M.V.F.—mitral valve flow in cubic centimeters per diastolic second.
A.V.F.—aortic valve flow in cubic centimeters per systolic second.
V.F.G. (ventricular filling gradient)—mean pressure difference in mm. Hg between left atrium and left ventricle during filling.
S.P.G. (systolic pressure gradient)—mean pressure difference in mm. Hg between left ventricle and aorta during systolic ejection.
C.O.—cardiac output in liters per minute.
V.F.P.—ventricular filling period in diastolic seconds per minute.
S.E.P.—systolic ejection period in systolic seconds per minute.
D—average duration in seconds of one ventricular filling.
S—average duration in seconds of one ventricular ejection.
H.R.—heart rate in beats per minute.



A. *B.*

Fig. 1.—Relation of systolic ejection period to systole, and of ventricular filling period to diastole. *A*, Simultaneous recordings in aortic stenosis of brachial artery and left ventricular pressures, and Lead II of the electrocardiogram. Systolic ejection period (black square). *B*, Simultaneous recordings in mitral stenosis of left atrial and left ventricular pressures. Ventricular filling period (black square).

As shown in Fig. 1, the systolic ejection period and the ventricular filling period do not correspond exactly to systole and diastole, respectively.

The requisite data may be obtained by combined right and left heart catheterization,[2] brachial artery puncture, and collection of expired air. Cardiac output is determined by the Fick principle. If both mitral and aortic valve areas are to be estimated, cardiac output must be determined for each valve separately. Pressure tracings should be recorded either immediately before or immediately after the drawing of blood samples, while the expired air is still being collected. All samples and tracings should be obtained within a period of a few minutes with the patient in a steady state. The most accurate determination of the mean diastolic pressure gradient across the mitral valve is done by planimetry between the simultaneously recorded left atrial and left ventricular pressure tracings obtained by left heart catheterization, using a double-adapter needle.[3] Simultaneous recording is especially important if the rhythm is irregular. The average

duration of ventricular filling and ventricular ejection and the heart rate are determined directly from the tracing, preferably by averaging the data of ten consecutive cardiac cycles. The mean systolic pressure gradient across the aortic

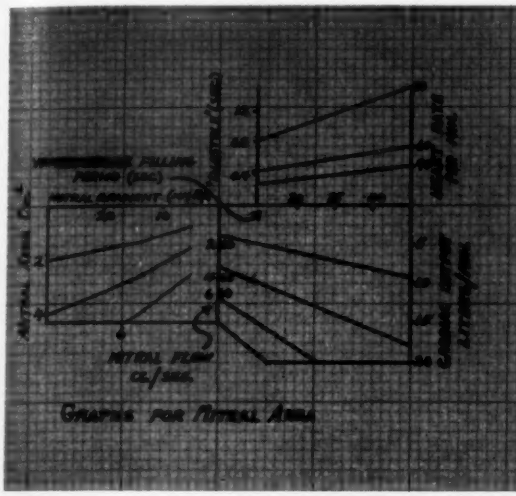


Fig. 2.

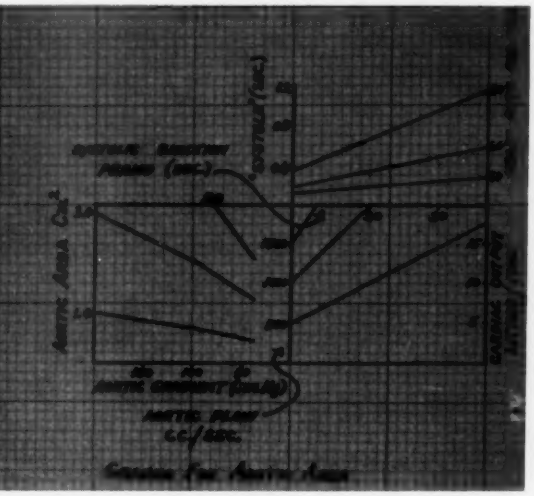


Fig. 3.

Fig. 2.—Graphs for the determination of mitral valve area. See text for explanation.
Fig. 3.—Graphs for the determination of aortic valve area. See text for explanation.

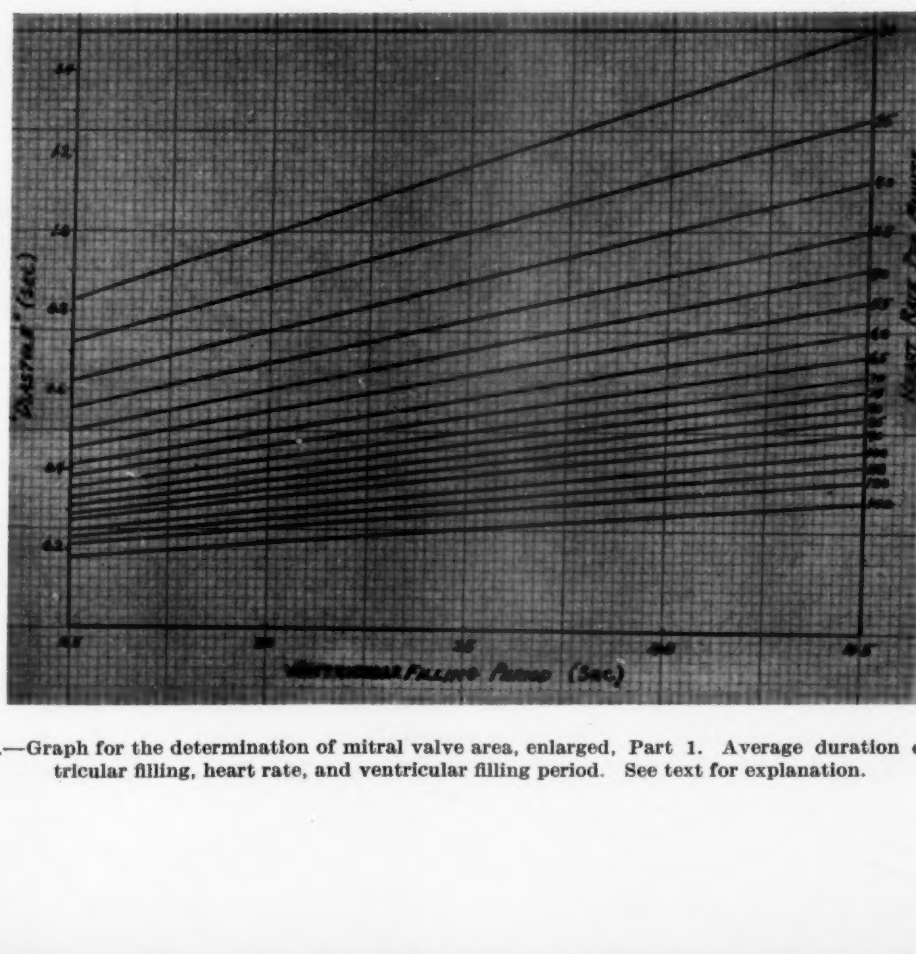


Fig. 4.—Graph for the determination of mitral valve area, enlarged, Part 1. Average duration of ventricular filling, heart rate, and ventricular filling period. See text for explanation.

valve is obtained by planimetry from the simultaneously recorded left ventricular and aortic (or brachial artery) pressure curves. Here, also, simultaneous recordings are especially important in the presence of irregular rhythm.

In order to simplify the arithmetic involved, we have constructed graphs of the Gorlin and Gorlin equations. Figs. 2 and 3 show graphs for determination

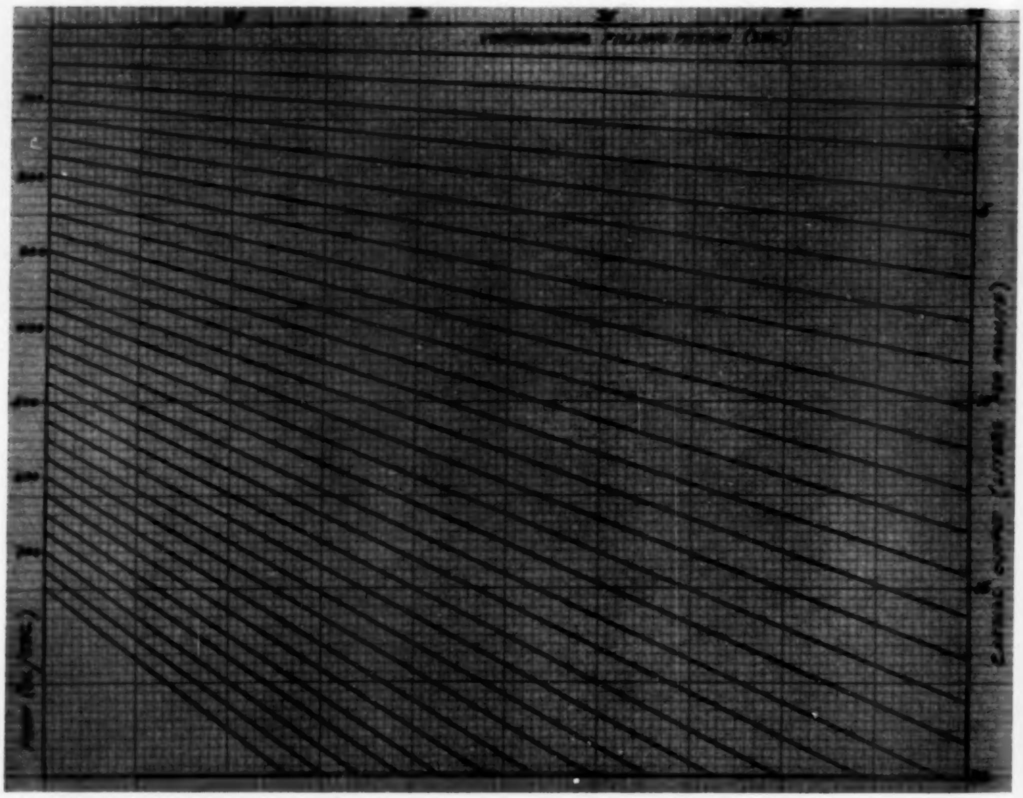


Fig. 5.—Graph for the determination of mitral valve area, enlarged, Part 2. Ventricular filling period, cardiac output, and mitral valve flow. See text for explanation.

of mitral and aortic valve areas. In these figures, many of the lines have been omitted for clarity. Figs. 4 through 9 are the component parts of these graphs, sufficiently enlarged to be useful. Rather large values of cardiac output have been included so that the graphs may be used in connection with exercise studies.

The mitral valve area graph is used as follows: Start at the line labeled *diastole*, and select the grid line which corresponds to the observed average duration of ventricular filling. Proceed horizontally to the right until the diagonal line closest to the observed heart rate is intersected. From this intersection,

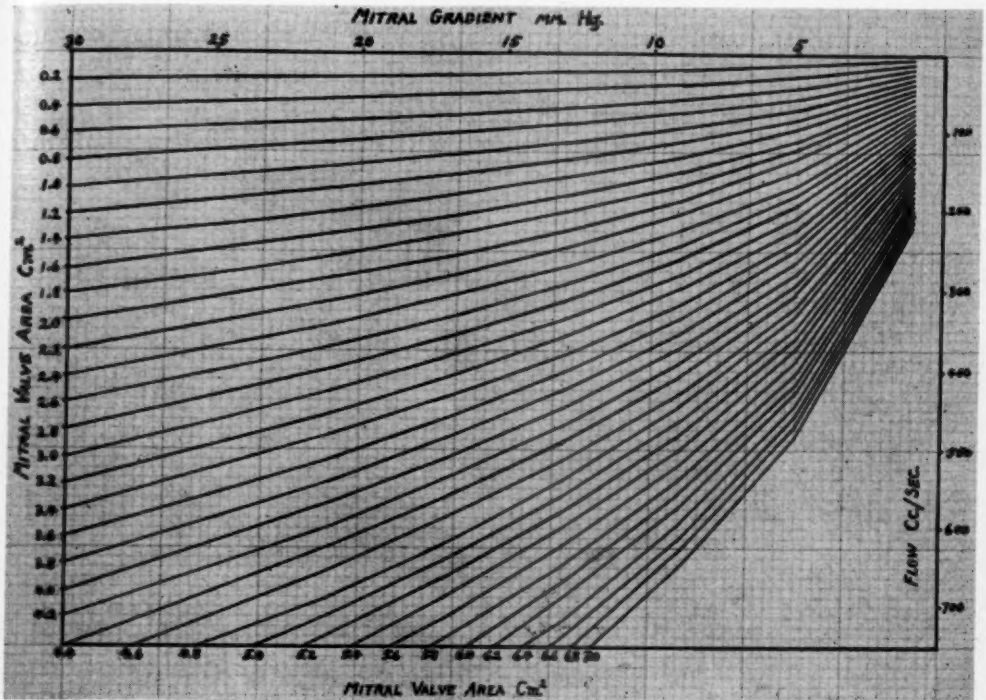


Fig. 6.—Graph for the determination of mitral valve area, enlarged, Part 3. Mitral valve flow, ventricular filling gradient, and mitral valve area. See text for explanation.

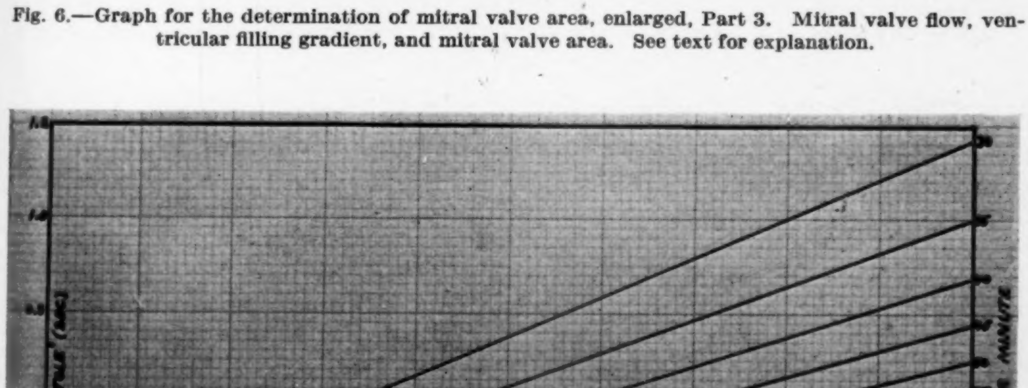


Fig. 7.—Graph for the determination of aortic valve area, enlarged, Part 1. Average duration of ventricular ejection, heart rate, and systolic ejection period. See text for explanation.

drop vertically to the line labeled ***ventricular filling period.*** Continue to drop vertically until the grid line corresponding to the observed cardiac output is intersected. From this intersection, follow the nearest diagonal line left to the line labeled *flow.* Follow the proper *flow* grid line to the left until the grid line corresponding to the observed mitral gradient is intersected. From this intersection, follow the nearest curved line to its end, and read the mitral valve area.

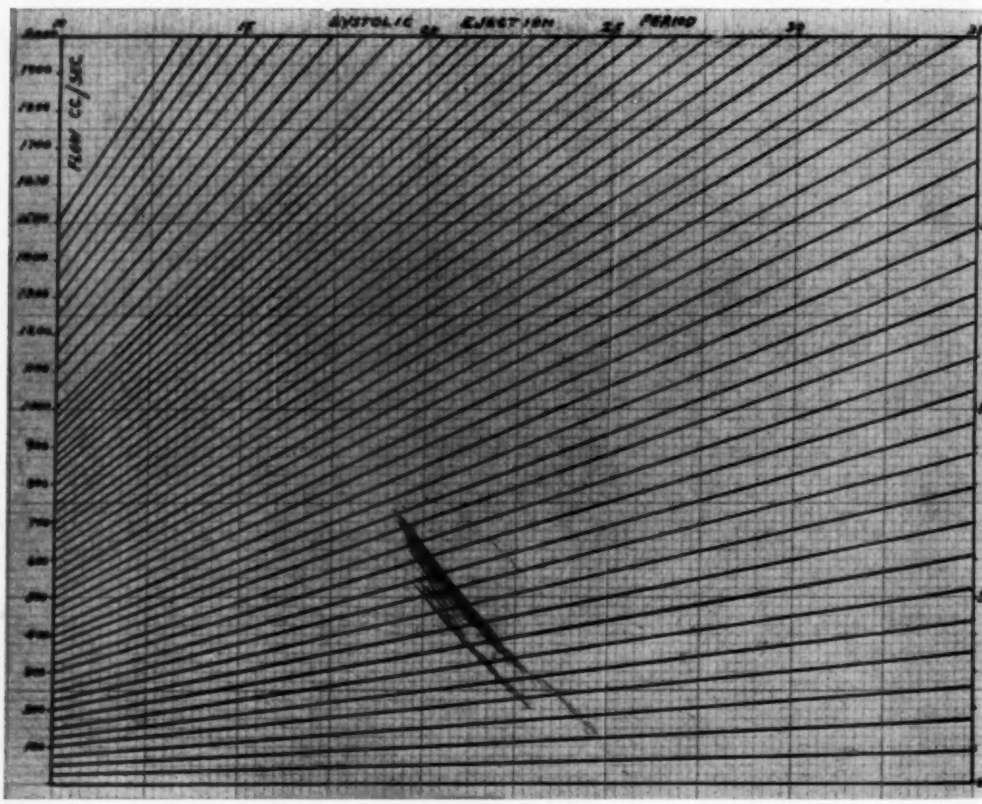


Fig. 8.—Graph for the determination of aortic valve area, enlarged, Part 2. Systolic ejection period, cardiac output, and aortic valve flow. See text for explanation.

The aortic valve area graph is used as follows: Start at the point on the line labeled *systole* which corresponds to the average duration of ventricular ejection. Proceed horizontally to the right until the diagonal line closest to the observed heart rate is intersected. From this intersection, drop vertically to the line labeled *systolic ejection period.* Continue to drop vertically until the grid line corresponding to the observed cardiac output is intersected. From this intersection, follow the nearest diagonal line to the left to the line labeled *flow.*

Follow the proper *flow* grid line to the left until the grid line corresponding to the observed aortic valve gradient is intersected. From this intersection, follow the nearest curved line to its end, and read the aortic valve area.

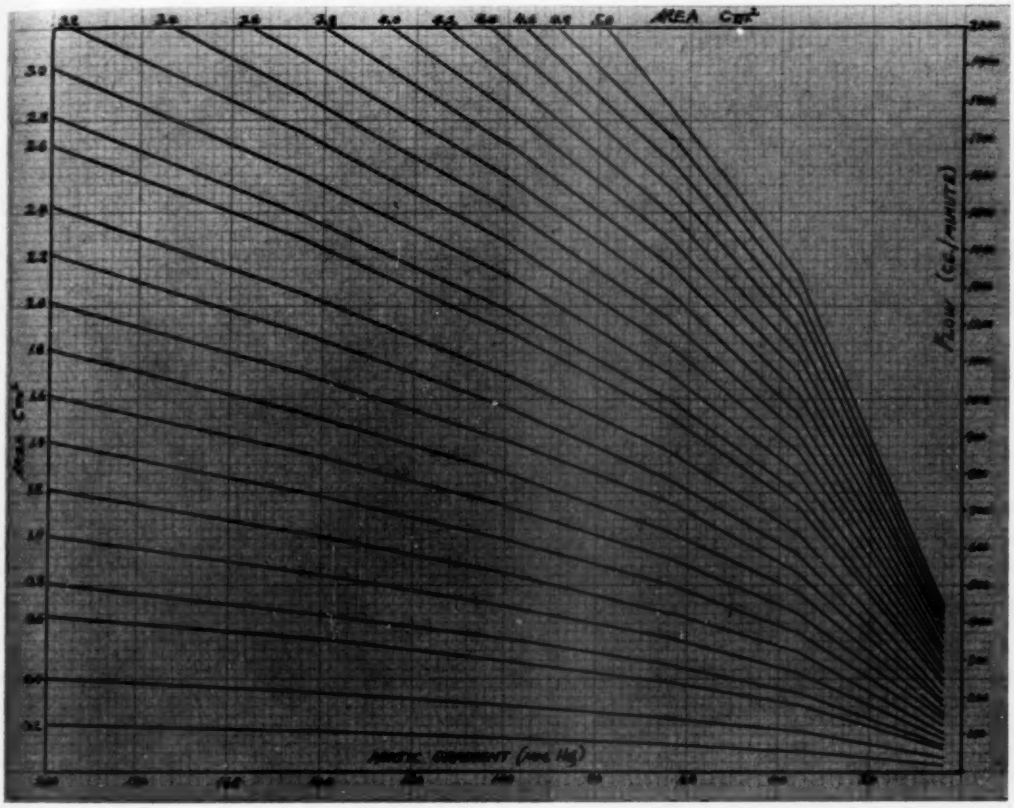


Fig. 9.—Graph for the determination of aortic valve area, enlarged, Part 3. Aortic valve flow, systolic pressure gradient, and aortic valve area. See text for explanation.

SUMMARY

An indirect method of estimating the area of orifice of stenotic aortic and mitral valves has been described by Gorlin and Gorlin.[1] The method is based on theoretical hydraulic considerations, and on data obtained by cardiac catheterization and brachial artery puncture, and has been modified by the application of combined right and left heart catheterization. A graphic method is presented whereby calculation of the valve areas by the Gorlin and Gorlin formulae is simplified.

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Tetralogy of Fallot With Absent Left Pulmonary Artery: Report of a Case With Anomalous Development of the Right Hilar Vasculature and Nonfunctioning Right Lung

O'Neill Barrett, Jr., Captain, MC, USA, and Weldon J. Walker, Colonel, MC, USA, Fort Sam Houston, Tex.

Since the original report by Thomas,[1] in 1941, a total of 20 cases of tetralogy of Fallot with absent pulmonary artery have been described.[2] It is the purpose of this paper to present another case which, in addition, manifests a previously undescribed failure of branching of the right pulmonary artery with a non-functioning right lung.

CASE REPORT

A 6-week-old white male infant was seen because of mild cyanosis and a continuous murmur which had been present since birth. The infant had manifested increasing dyspnea, listlessness, and a weak cry. Physical examination revealed a well-developed, fairly well-nourished infant with moderate cyanosis of equal intensity in the upper and lower extremities. No clubbing was noted. Respiratory rate was 26 per minute and lung fields were clear.

Cardiovascular examination revealed a heart rate of 170 per minute, apex beat in the fifth intercostal space in the left anterior axillary line and a Grade 3 systolic and diastolic murmur best heard in the third left intercostal space. There was gallop rhythm and a diminished pulmonic second sound. Peripheral pulses were normal. The liver was palpable 2 fingerbreadths below the right costal margin. Laboratory data revealed a normal blood count and urinalysis. An electrocardiogram showed right ventricular hypertrophy. Cardiac fluoroscopy revealed elevation of the right diaphragm and a density in the region of the right superior mediastinum which did not appear to pulsate. There was generalized cardiac enlargement, apparent prominence of the pulmonary artery, and approximately normal pulmonary vascular markings in the left lung, which was much better aerated than the right.

Digitalis was administered because of suspected early cardiac decompensation. Cyanosis was most pronounced following feedings or episodes of crying. The infant's condition remained stable during the first hospital week and angiocardiography was scheduled. However, on the eleventh hospital day the infant suddenly developed severe respiratory distress with bilateral râles and intercostal retractions, and expired 14 hours later despite increased digitalis, oxygen and antibiotic therapy.

From the Cardiovascular Service, Brooke Army Hospital, Fort Sam Houston, Tex.
Received for publication Aug. 20, 1957.

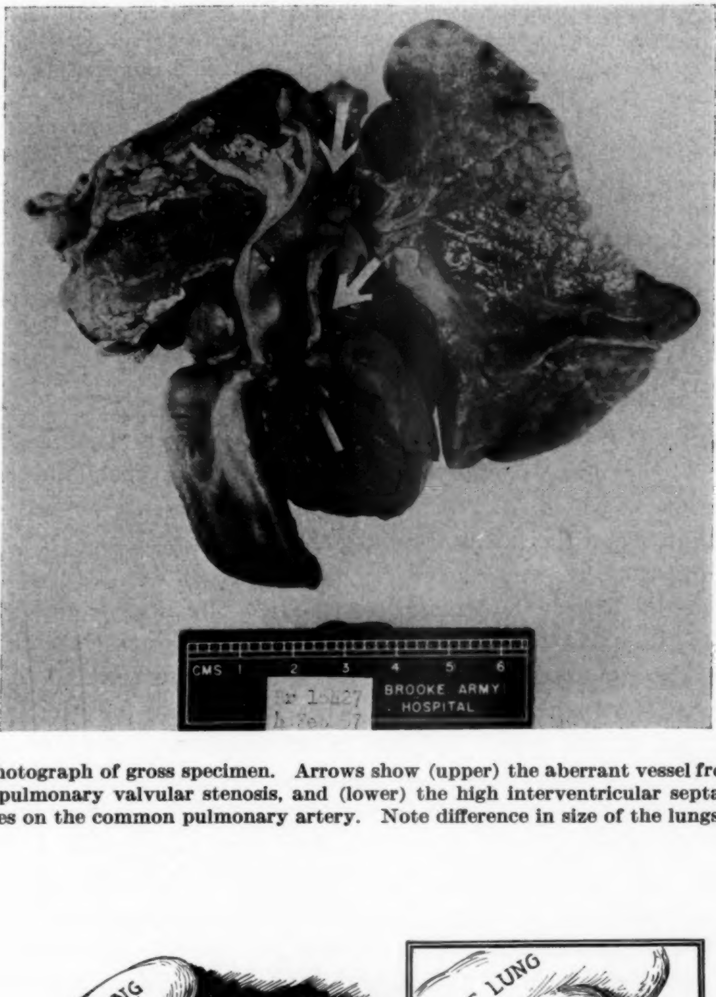

Fig. 1.—Photograph of gross specimen. Arrows show (upper) the aberrant vessel from aorta to left lung, (middle) pulmonary valvular stenosis, and (lower) the high interventricular septal defect. The middle arrow lies on the common pulmonary artery. Note difference in size of the lungs.

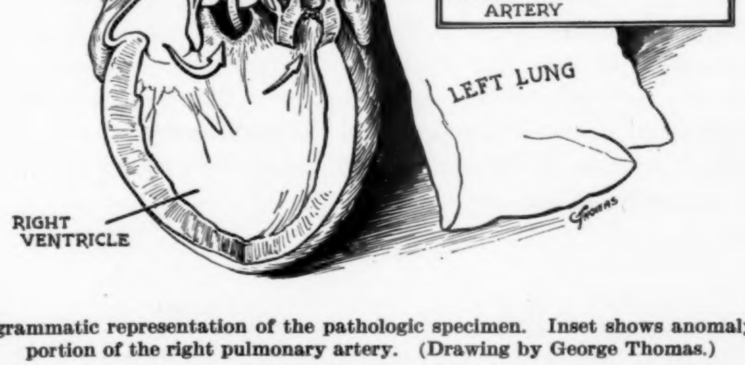

Fig. 2.—Diagrammatic representation of the pathologic specimen. Inset shows anomaly of the distal portion of the right pulmonary artery. (Drawing by George Thomas.)

Autopsy.—The heart at autopsy weighed 40 grams. There was right ventricular hypertrophy and a small, high interventricular septal defect, 1.2 cm. in diameter (Fig. 1). The foramen ovale was patent. The pulmonary valve was stenotic and the cusps could not be identified. Beyond the stenosis the pulmonary artery was markedly dilated, measuring 2 cm. in its greatest diameter. It extended as a single unbranching sausage-like trunk to the region of the right hilus. At its distal portion the vessel failed to branch and terminated abruptly in a septum with several small sieve-like perforations (Fig. 2). The diameter of the aorta was 1.25 cm. and the arch was on the left side. A blood vessel, 0.4 cm. in diameter, arose from the aortic arch and entered directly into the upper portion of the left lung. The left lung appeared grossly normal except for absence of the pulmonary artery and its branches. The right lung was small and atelectatic. Microscopic examination of sections of the right lung revealed only slight thickening of the arteries just beyond the hilus, and generalized atelectasis.

DISCUSSION

Abnormalities of the pulmonary arteries have been described previously. Manhoff and Howe[3] have suggested a classification for such abnormalities, related to the stage at which the normal growth process is interrupted. They have pointed out that, when the left pulmonary artery is absent, the anomalous artery to the left lung may represent either a persistent ductus arteriosus or hypertrophied bronchial arteries. Maier[4] has stressed the importance of the dorsal branches from the aorta to the pulmonary vascular plexus (bronchial arteries). McKim and Wigglesworth[5] have further stressed the fact that, in cases of absent left pulmonary artery, the ductus arteriosus may remain patent, and they have reported one case of this type. Because of the location of the aberrant vessel to the left lung, our case was thought to represent a patent ductus arteriosus. The incidence of right-sided aortic arch in tetralogy of Fallot is approximately 20 to 25 per cent.[6] In tetralogy of Fallot with absent left pulmonary artery, the incidence is 60 per cent in reported cases.[2] Our patient had a left-sided aortic arch.

It is of interest that, in our patient, life was maintained for 7 weeks by the functioning left lung which lacked a pulmonary artery. The main pulmonary artery terminated abruptly at the right hilum in a septum containing several small perforations which appeared to allow some blood to flow into the arteries distal to this septum. These arteries were small but grossly and microscopically normal. Microscopic sections of the septum revealed normal arterial structure except for some apparent immaturity of the subintimal connective tissue.

The cause for atelectasis of the right lung was not evident. However, it could be explained on the basis of Jäykkä's[7] concept that capillary erection, effected by increased liquid pressure in the pulmonary artery, plays an important part in producing expansion of the lung in the newborn infant. In our patient such pulmonary artery pressure to the right lung was damped both by a stenotic pulmonary valve and a septal obstruction of the pulmonary artery. In addition, there was no ductus connected to the common pulmonary artery to aid in effecting such capillary erection at the time of birth.

SUMMARY

A case of tetralogy of Fallot with absence of the left pulmonary artery and nonfunctioning right lung with a previously undescribed developmental anomaly

of the right hilar vasculature is reported. Life was maintained for 7 weeks by the left lung which received blood from the aorta through what appeared to be a patent ductus arteriosus.

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Persistent Truncus Arteriosus: Report of a Case With Atypical Radiologic Features

Monty J. Goldberg, M.B., B.Ch., and Maurice McGregor, M.D., M.R.C.P.
Johannesburg, South Africa

To judge from authoritative descriptions, the diagnostic picture of persistent truncus arteriosus is distinctive. Essentially, the pattern is described as one of "central cyanosis, enlargement of both ventricles, particularly the left, a single second heart sound, absence of the pulmonary arc, and pulmonary plethora."[1] However, variations in this clinical pattern may occur. A case was recently encountered where these criteria were satisfied, except for two unusual features. First, there was marked fullness of the pulmonary arc, and, secondly, the second heart sound was apparently split.

Thus the findings closely simulated those seen in cases of pulmonary hypertension associated with a patent ductus arteriosus, an atrial septal defect, or a ventricular septal defect. The history and findings are reported in some detail below in the belief that a wider knowledge of all variants of the typical pattern will be helpful in avoiding diagnostic errors in the future.

CLINICAL DATA

A European male, aged 16 years, had the sole complaint of moderate effort dyspnea since early childhood. He was a thinly built adolescent of average height, without arachnodactyly or a high arched palate. Slight cyanosis of equal degree in the upper and lower extremities was evident. The pulse was normal in character, the blood pressure was 120/60 mm. Hg, and the jugular venous pressure, although not elevated, showed a markedly accentuated "a" wave. The maximum cardiac impulse was displaced into the axilla and was of a left ventricular type. There was also a marked systolic heave in the left parasternal area and a palpable pulsation over the pulmonary area. The first sound at the mitral area was moderately increased, while the second sound at the pulmonary area was very loud, and closely split (Fig. 1). In addition, an early systolic ejection click of great intensity was audible and easily palpable. Medial to the apex and at the left sternal border there was a fourth heart sound, and in the second intercostal space 1.5 inches from the left sternal border there was a long, Grade 3 decrescendo early diastolic murmur. Electrocardiograms (Fig. 2) were thought to indicate combined ventricular hypertrophy. Radiologic investigation (Fig. 3) revealed a heart lying mainly in the left hemithorax. Lung vascularity

From the Cardiopulmonary Research Unit of the Council for Scientific and Industrial Research and the Department of Medicine of the Witwatersrand University, and the Johannesburg Hospital, Johannesburg, South Africa.

Received for publication Aug. 22, 1957.

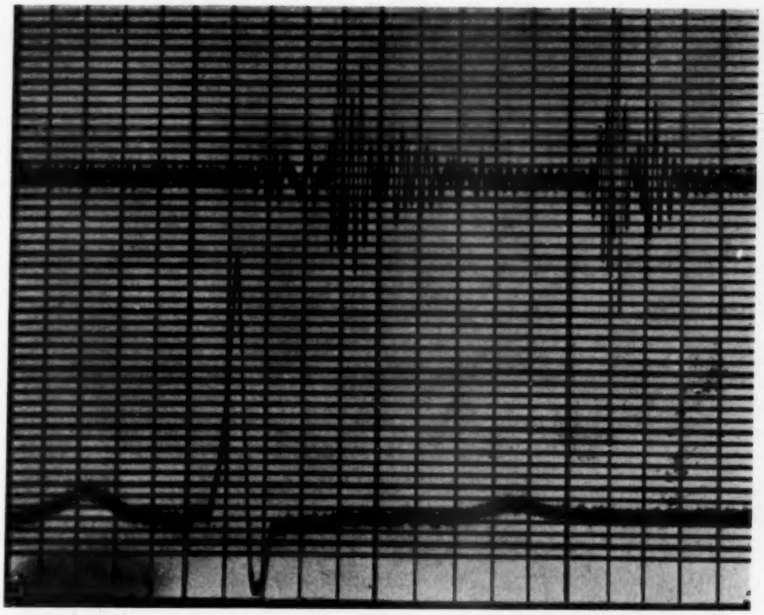

Fig. 1.—Phonocardiogram in pulmonic area. Note apparent splitting of second heart sound and early systolic ejection click.

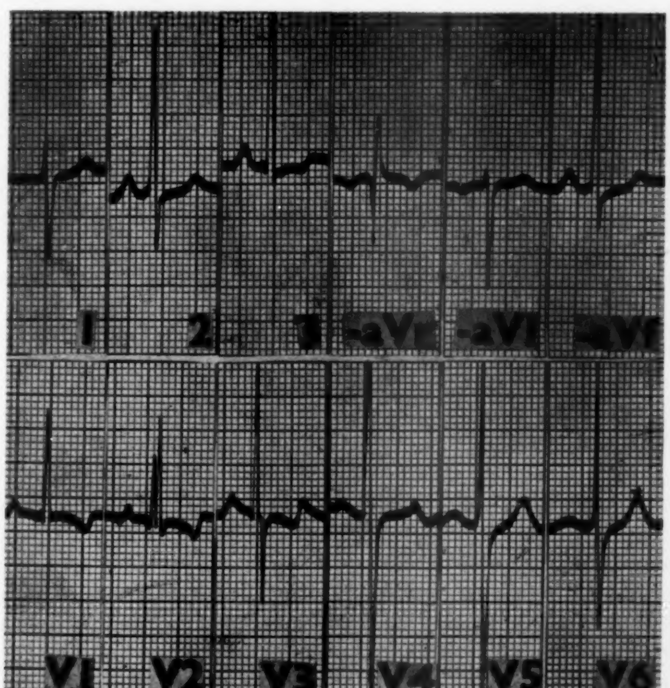

Fig. 2.—Electrocardiogram. 1 mv. = 1 cm.

was within normal limits. The pulmonary artery was more prominent than could be accounted for by rotation and there was an unusually large aortic indentation of the barium-filled esophagus. There was enlargement of both ventricles but no definite atrial enlargement, and fluoroscopy showed markedly collapsing pulsations of the pulmonary artery segment. Ear oximetry confirmed unsaturation at rest (±80 per cent). The oxygen saturation fell to below 30 per cent on effort, and rose to a normal level* of 97 per cent after breathing 100 per cent oxygen for 5 minutes.

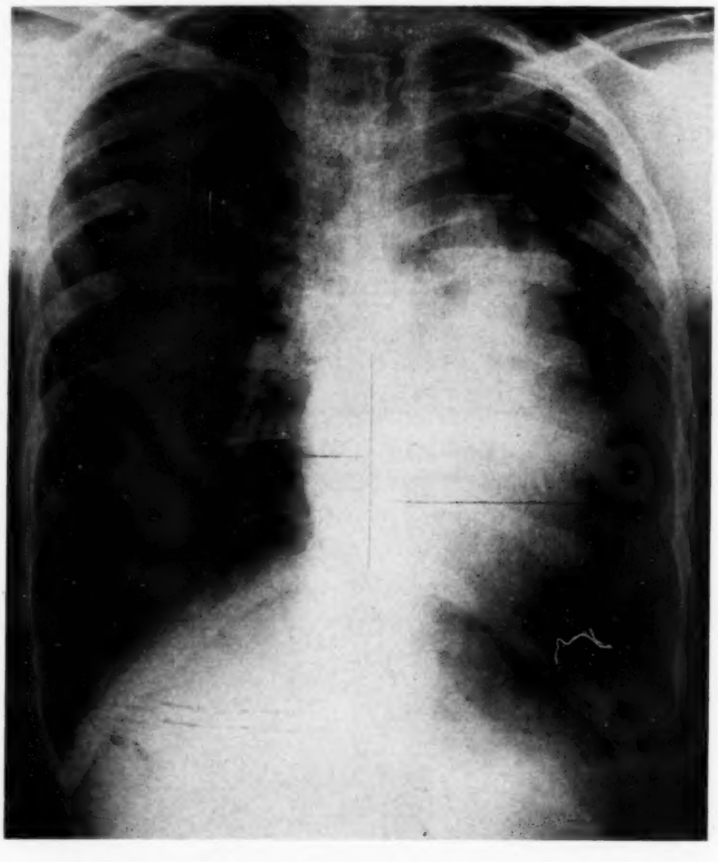

Fig. 3.—Teleroentgenogram. Note the prominence of the pulmonary arc, and apparently normal lung fields.

On cardiac catheterization the catheter passed easily into the main and right pulmonary arteries. At the level of the main pulmonary artery a considerable admixture of arterialized blood was shown. The catheter was easily passed down the aorta, where the systolic pressure was 110 mm. Hg. This pressure was identical in the right ventricle and the main pulmonary artery. The oxygen saturation of samples taken simultaneously from the descending aorta and right brachial artery was 86 per cent in both. Injection of Evans blue dye just above the pulmonary valve demonstrated a right-to-left shunt above this site, as shown by oximeter. Finally, systemic and pulmonary artery flow, as measured by the Fick principle,† were shown to be 2.47 and 6.57 liters per minute, respectively, and pulmonary arteriolar resistance was moderately elevated (609 dynes/sec./cm.$^{-5}$).

***Within the limits of accuracy of the method. Waters Conley Absolute Reading Ear Oximeter.**
†Assumed pulmonary venous oxygen saturation of 93 per cent.

These findings demonstrated the presence of some sort of communication between aorta and pulmonary artery since there was evidence of bidirectional shunting above the level of the pulmonary valve. The absence of differential cyanosis indicated this was not a ductus arteriosus, while a persistent truncus arteriosus was excluded on the presence of a prominent "main" pulmonary artery with a split second heart sound. It was felt, therefore, that the most likely diagnosis was an aortic-pulmonary septal defect. In order to confirm this diagnosis, retrograde arteriography was carried out and dye was injected just above the aortic valve. Because of very rapid dilution the results were not very satisfactory, but they did demonstrate simultaneous filling of the pulmonary artery and descending aorta, thus tending to confirm the diagnosis of aortic-pulmonary artery septal defect.

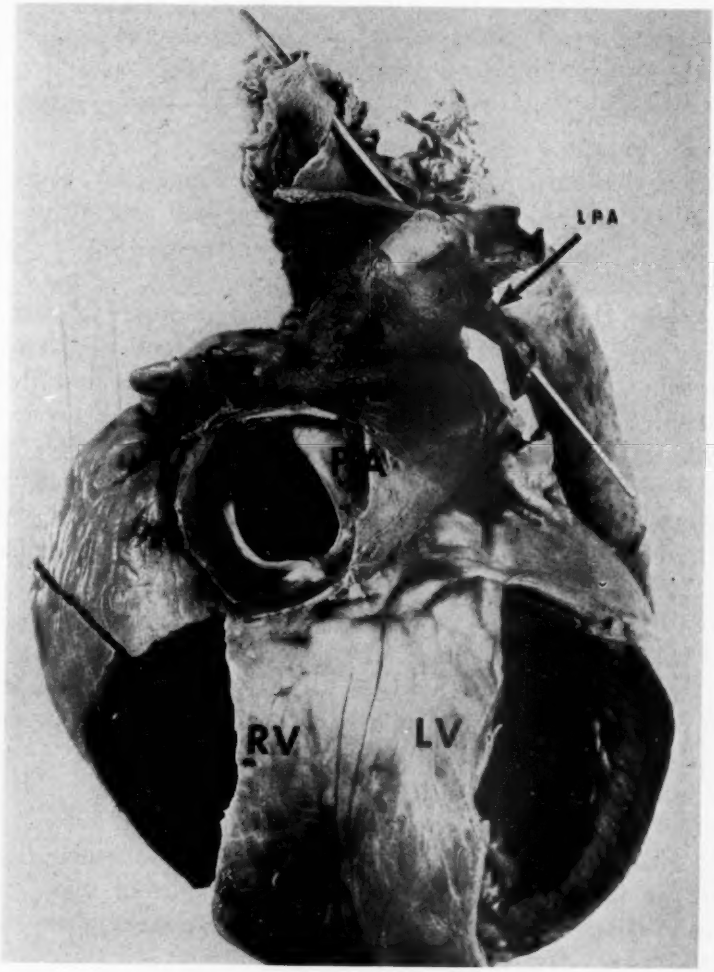

Fig. 4.—Anterior surface of heart at autopsy. The line of surgical incision of the pulmonary artery has been extended, and below this incision the fistula leading into the truncus can be seen. The apparent lower border of this fistula consists of a cusp of the common basal valve. *LPA* = Left pulmonary artery arising from aortic arch. *A* = Ascending aorta. *RV* = Right ventricle. *LV* = Left ventricle.

Inasmuch as there was clinical evidence of deterioration, and since the ultimate prognosis was considered to be poor, it was decided that an attempt should be made to occlude the defect. The patient was operated upon under hypothermia and the heart exposed through a sternal-splitting incision. A tremendous pulmonary artery and a smaller aorta joining about 4 cm. above

the aortic valve were found, but no lower border to this communication could be identified. However, since it was thought that the lower margin of the fistula was probably present just at the level of the valves, an attempt was made to close the fistula. Under circulatory arrest the pulmonary artery was incised longitudinally and sutures were passed between the two raphe which indicated the edges of the aortic pulmonary septum. The pulmonary artery was then closed and the circulation was restarted. At this stage ventricular fibrillation developed and, although this was stopped, the patient eventually died with a grossly dilated heart.

Autopsy revealed an interventricular septal defect with an overriding 3-cusped basal valve leading into a common truncus. Almost at its origin the truncus opened through a large fistula into a grossly dilated pulmonary artery (Fig. 4). Although this vessel was in the position of a dilated main pulmonary artery, it arose from the truncus and passed a normal course to the right lung. The left lung was supplied by a small vessel from the aortic arch arising just opposite the origin of the innominate artery. There was no other arterial abnormality and the pulmonary venous return was normal.

DISCUSSION

The death of this patient is attributable to the fact that, although a defect of the aortic-pulmonary septum was correctly diagnosed, the authors were misled by the prominent "main" pulmonary artery into discounting the presence of a truncus and ventricular septal defect. Developmentally, simple fistulous communication between the aorta and pulmonary artery is closely related to persistent truncus arteriosus, since the former represents a partial, and the latter a complete, failure of closure of the truncoconal septum. Thus, Collett and Edwards[2] have reasonably included aortic-pulmonary fistulas as a fifth type of persistent truncus. However, while the simple fistula is capable of surgical correction, the persistent truncus is not and it becomes a vital matter to distinguish between them.

This distinction should not be difficult in those varieties of truncus which conform to the classical radiologic description of a hollow pulmonary bay and "sitting duck" silhouette.[3] However, there is evidence that there may be many exceptions to this description. Persistent truncus has been divided by Collett and Edwards into 4 principal types. The pulmonary segment can be expected to be absent or small in their Types 2, 3, and 4 in which there is a complete absence of any main pulmonary trunk. However, in their Type 1 a main pulmonary trunk and aorta arise from a short common origin, and in some of these a prominent pulmonary artery segment might be anticipated. It is most significant that of 77 cases of truncus reviewed by Collett and Edwards 35 fell into this category, although it is not possible to ascertain from their report whether this type does, in fact, differ radiologically from the other two. In 2 recently reported cases of this type the pulmonary artery segment appears normal rather than reduced.[4]

The case reported here most closely falls into Collett and Edwards' Type 1, although its exact counterpart cannot be found in the available literature. In our case a large single pulmonary trunk arises from the anterior surface of the common truncus. This vessel supplies only the right lung, while the vessel to the left lung arises from the aortic arch. In such a case it is difficult to see how the presence of the truncus could have been proved. Radiology favored a simple fistula, in which condition a full pulmonary segment appears invariable.[3,5-9] At catheterization a sample could not be obtained high in the right ventricle because

of extreme cardiac irritability in this region. However, even if found, an increase in oxygen content at this site might have been reasonably expected in the presence of a known regurgitant lesion. The apparent splitting of the second heart sound was interpreted as evidence of two separate valves. In retrospect, the fact that the second element was smaller was inconsistent with the preoperative diagnosis. The actual reason for the apparent splitting, however, is not apparent.

In conclusion it must be remarked that the differentiation of patent ductus arteriosus or isolated ventricular septal defect might also have been most difficult had there not been some right-to-left shunt through the defect, and there are cases in which only thoracotomy can establish the diagnosis. The possibility of a truncus should be borne in mind even in the presence of a prominent pulmonary arc. Failure to define the lower border of an apparent aortic septal defect at surgery should then lead to the diagnosis of persistent truncus.

SUMMARY

A case of persistent truncus arteriosus is reported in which the diagnosis was missed because of two unusual features. These were a full pulmonary artery segment and apparent splitting of the second heart sound. This case is reported to correct the widespread impression that a hollow pulmonary bay characterizes all types of persistent truncus.

Our thanks are due to Dr. Josse Kaye, his staff in the Department of Radiology, and to Dr. David Adler, Assistant Thoracic Surgeon, Johannesburg Hospital, for their helpful cooperation, to Dr. T. H. Bothwell for suggestions in the writing of this report, and to Prof. G. A. Elliott in whose department this work was carried out.

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Ebstein's Anomaly of the Tricuspid Valve: Anatomic Confirmation of Angiocardiographic Diagnosis

Albert D. Kistin, M.D., John M. Evans, M.D., and Alfred E. Brigulio, M.D.
Washington, D. C.

We recently reported[1] the diagnosis of Ebstein's anomaly of the tricuspid valve by angiocardiography, based on the previous study of Soloff and his associates,[2] who now have anatomic confirmation of their case.[3] The patient who was the subject of our report has since died of myocardial infarction, and the predicted anomaly has been demonstrated.

This 31-year-old law student had a brother who had a myocardial infarct at the age of 34, and his father, now 58 years old, had had myocardial infarcts at age 52 and again at 54. The patient returned to the George Washington University Hospital on April 4, 1956, with pain in the interscapular region and both arms. An electrocardiogram showed definite changes from the previous electrocardiogram and was considered diagnostic of recent myocardial infarction of the anterior wall. The body temperature was 37°C. on the first hospital day, 38° to 39°C. during the second to fifth hospital days, and normal thereafter. The white blood count was 21,900 per cubic millimeter with 77 per cent neutrophils, and the serum glutamic oxalacetic transaminase was 166 units. The blood pressure on admission was 94/80 mm. Hg, and on the third hospital day it was 84/68 mm. Hg. The patient received anticoagulants and for a time, Wyamine (mephentermine). He felt well from the eighth to the eighteenth hospital day. On the eighteenth hospital day he died while having a bowel movement.

The description of the heart was as follows: The heart weighed 420 grams, and presented a greatly enlarged right auricular appendage. The visceral pericardium contained a moderate amount of fat. The apex was rounded. The right auricle and appendage were greatly dilated. The interauricular foramen was not patent, and no thrombi were noted. The tricuspid valve had a circumference of 16.5 cm. The cusps were thin and supple, and presented numerous fenestrations at their margins and base of insertion. The posterior cusp inserted 2.9 cm. below the annulus fibrosus on the right ventricle. There was a depressed, wrinkled area above the depressed valve insertion. The right ventricle was very small, and measured from 0.2 to 0.4 cm. in thickness. The endocardium was smooth and glistening. The papillary muscles were slightly thickened; the chordae tendineae were likewise slightly thickened. The pulmonic valve had a circumference

From the Department of Medicine, George Washington University Hospital and George Washington University School of Medicine, Washington, D. C.
Received for publication Sept. 12, 1957.

of 7.1 cm. The pulmonary artery had a circumference of 3.8 cm. at the bifurcation. The left auricle and appendage were not dilated. The mitral valve had a circumference of 9.2 cm., the cusps being thin and supple. The left ventricle measured up to 1.5 cm. in thickness. Section through the myocardium presented a yellow, soft area measuring up to 4 cm. in diameter, in the anterior two thirds of the interventricular septum, mainly in the left subendocardial region, which was prolonged for a small distance onto the anterior wall of the left ventricle. The endocardium was smooth and glistening. The papillary muscles were grossly normal, as were the chordae. The aortic valve had a circumference of 6.7 cm., and the cusps were thin and supple. The ascending aorta presented two longitudinally arranged areas composed of slightly elevated, yellow, firm plaques measuring up to 0.2 cm. in diameter. The coronary ostia were patent. The left circumflex coronary artery, 0.3 cm. from its origin, was calcific and occluded.

The anatomic diagnoses were: (1) acute anterior septal myocardial infarct; (2) occlusion of left circumflex branch of coronary artery, and (3) Ebstein's anomaly of the tricuspid valve.

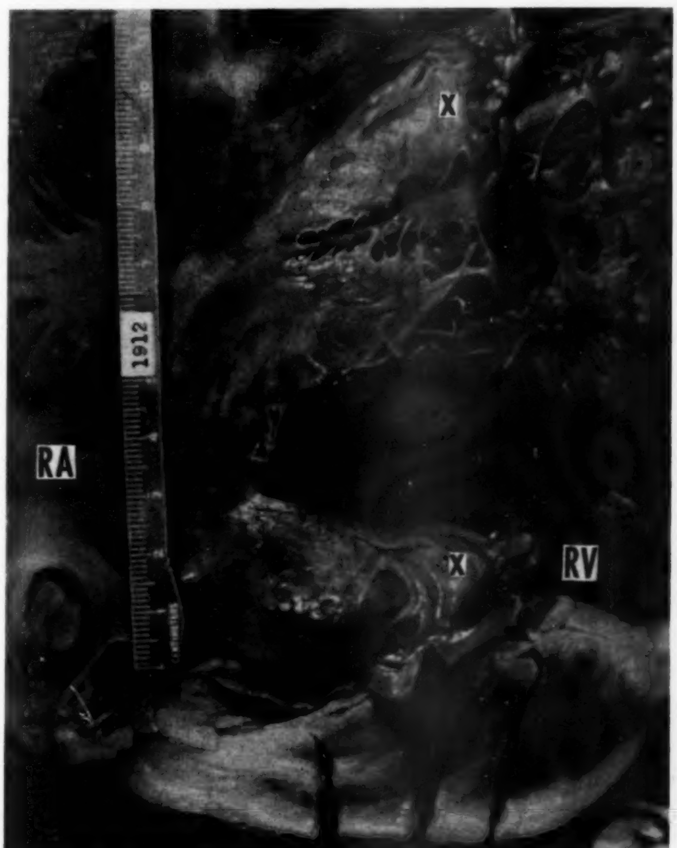

Fig. 1.—Photograph of the heart, looking down on right atrium, tricuspid valve, and right ventricle. *RA*—right atrium. Tip of arrow at original atrioventricular ring (annulus fibrosus). *X*—peripheral extensions and attachments of tricuspid valve. Note absence of normal long chordae tendineae. *RV*—right ventricle.

The illustration of the heart in Fig. 1 shows the right atrium, the tricuspid valve with a line at the original A-V ring and the low attachments characteristic of the anomaly, and a part of the right ventricle. We judge that the notch demon-

strated in the angiocardiograms represents a constriction during systole between the proximal atrialized portion of right ventricle (left of RV in the illustration) and a small right ventricle (RV).

SUMMARY AND CONCLUSION

The angiocardiographic diagnosis of Ebstein's anomaly of the tricuspid valve is anatomically confirmed in one patient.

The authors gratefully acknowledge the cooperation of Dr. Thomas M. Peery in providing the results of the histopathologic examination.

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The Electrocardiogram in Interatrial Septal Defects and Its Correlation With Hemodynamics

Jorge Martins de Oliveira, M.D., and Henry A. Zimmerman, M.D.***
Cleveland, Ohio

Since the works of Routier and de Balsac[1] and Vizcaino and associates,[2] many authors have emphasized the frequency with which the electrocardiographic pattern of incomplete right bundle branch block is found in patients with an interatrial septal defect. These authors considered the presence of a late R wave in the right precordial leads as representing disturbance in conduction of the right branch of the bundle of His, and this is still the concept accepted by many authors. It is our opinion that, in the great majority of cases, this morphology in V_1 and V_2 does not mean any disturbance of conduction of the right bundle branch itself, but rather of the basal portions of the free wall of the right ventricle and perhaps includes the higher parts of the interventricular septum. Cabrera and Monroy[3] consider this late R-wave morphology in V_1 as representing diastolic overloading of the right ventricle. This concept is also subject to criticism, since this pattern has been found in many cases of pure pulmonic stenosis, while in some patients with interatrial septal defect and anomalous pulmonary venous drainage (in which the overloading is definitely of the diastolic type), such morphology has not been found. Limon Lason,[4] Walker,[5] and others tried to establish a comparison between the pattern of the QRS complex in V_1 and V_2 and the pressures in the right ventricular chamber. They demonstrated that, when the pressures in the right ventricle reached very high levels, the morphology then found was similar to that which one sees in systolic overloading, as for example in pulmonic stenosis and tetralogy of Fallot.

With the advent of open heart surgery, it became possible to evaluate with accuracy the postoperative electrocardiographic changes, since this surgical procedure leaves no doubt about complete closure of the septal defect.

MATERIAL AND METHODS

The present study is based on a series of 44 cases of interauricular septal defect proved by cardiac catheterization and/or surgery. Of the 32 patients operated, 15 were operated under

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Received for publication Sept. 13, 1957.

*Fellow in Cardiovascular Diseases, Marie L. Coakley Cardiovascular Laboratory, St. Vincent Charity Hospital, Cleveland, Ohio.

**Director of the Marie L. Coakley Cardiovascular Laboratory, St. Vincent Charity Hospital, Cleveland, Ohio.

direct vision by Dr. Earle B. Kay. All cases were catheterized in the Marie L. Coakley Cardiovascular Laboratory at St. Vincent Charity Hospital in Cleveland, Ohio. All the electrocardiograms were analyzed by the authors under uniform standards, using the 12 classical leads. The criteria for the diagnosis of interatrial septal defect were based on: (1) an increase of at least 2 vol. per cent of oxygen in the right auricular blood, as compared with inferior and superior vena caval samples, (2) passage of the catheter through the defect, or (3) findings at surgery. In 3 cases confirmation was made by post-mortem examination. In 12 patients the electrocardiograms were carefully reviewed after closure of the defect. Cases in which any doubt could exist concerning the diagnosis of an interatrial septal defect were not considered. The presence of other associated cardiac anomalies in some of the patients will be stressed.

Of the 44 patients studied, 27 were females and 17 were males. Seven cases, or 15.9 per cent, had other cardiac anomalies: 3 cases with mitral stenosis; 2 cases with interventricular septal defect; 1 case with anomalous pulmonary venous drainage and pulmonic stenosis; and 1 case with the left inferior vena cava draining into the coronary sinus. The ages of the patients ranged from 3½ months to 48 years. The average age was 16 years.

RESULTS

In Fig. 1 is shown the distribution of P, QRS, and T vectors in the frontal plane.

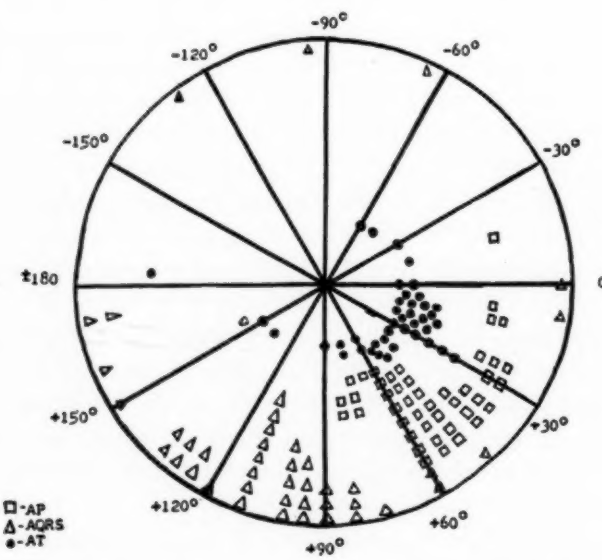


Fig. 1.—The distribution of P, QRS, and T vectors in the frontal plane in 44 patients with interatrial septal defect.

P Axis.—As can be seen in the great majority of these cases, 31 patients or 70.4 per cent, the P axis varied between $+30°$ and $+60°$. In 6 cases, or 13.8 per cent, there was a tendency of the auricular vector to deviate to the right (from $+65°$ to $+85°$). It is of interest to emphasize that in only 3 cases, in spite of the presence of other signs suggestive of right auricular overloading, the P vector was localized beyond $+75°$. This would appear to confirm the opinion that the rotation of the heart, more so than hypertrophy and dilatation of the right auricle, deviates the P axis to the right, as one sees in emphysema of the lungs.

In 7 cases, or 15.9 per cent, the auricular vector showed slight deviation to the left (from +25° to +10°), and in one patient marked left axis deviation (−15°) was found. It would seem important to emphasize that in these 7 cases there were other electrocardiographic signs that would also suggest left auricular overloading. In 2 there was associated mitral stenosis (Lutembacher's syndrome).

QRS Axis.—The ÂQRS was localized between +75° and +135° in 31 patients, 70.4 per cent. The systolic pressures in the right ventricle in this group varied between 22 and 114 mm. Hg. The average was 45.5 mm. Hg. It was not possible in these cases to establish an exact correlation between the systolic pressure in the right ventricular chamber and the degree of right axis deviation. However, a tendency of the mean axis to be localized between +110° and +135° was found in those cases that presented higher pressures.

In 4 patients, 9.0 per cent, there was a marked right axis deviation (between +150° and +170°). In 1 of these cases there was an associated pulmonic stenosis and an anomalous pulmonary venous drainage, and the systolic pressure in the right ventricle was 73 mm. Hg. In the other 3 patients, however, the systolic pressure in the right ventricular chamber did not exceed 42 mm. Hg.

In 5 patients, or 11.3 per cent, the mean vector of ventricular activation was localized between 0° and +60°. The systolic pressures in this group were between 22 and 42 mm. Hg.

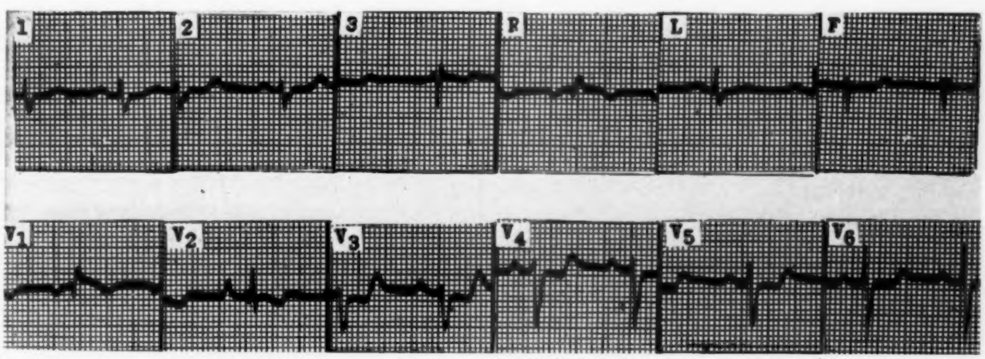


Fig. 2.—Shows the ÂQRS in the second sextant of Bailey in a case of interatrial septal defect with possible associated mitral insufficiency.

In the remaining 4 cases the ÂQRS was found in the second and third sextants of Bailey (between −65° and −130°), and the systolic pressures in the right ventricle varied between 25 and 36 mm. Hg (Fig. 2). Table I shows the correlation between ÂQRS and pressures in the right ventricle.

This localization of the axis in interatrial septal defect is relatively rare. Limon Lason[4] in 50 cases found this peculiar position in only 1 patient. Recently, Toscano Barbosa[6] showed the frequency with which the ÂQRS appears in such localization in patients with A-V communis or in cases of interatrial septal defect of the ostium primum type. Of our patients, 2 were operated by the closed technique and 2 have not been operated upon as of this date. In a future publication

we will report the findings in these cases and also in other cases of A-V communis which present these peculiar findings of localization of the ÂQRS.

The studies in cardiac catheterization in uncomplicated interatrial septal defect have shown that in these malformations the fundamental hemodynamic findings are: (1) increase in volume of blood to the right auricle, right ventricle, and pulmonary artery, (2) increase in work without significant changes in pressure in these chambers, (3) normal arterial blood saturation. As a consequence, the electrocardiographic alterations would be essentially related to increase in volume of blood-work, in opposition to what happens in other anomalies, such as pulmonic stenosis in which the fundamental hemodynamic factor is an increase in pressure-work without significant changes in blood volume in the right chambers (Ziegler[7]).

TABLE I. CORRELATION BETWEEN ÂQRS AND PRESSURES IN THE RIGHT VENTRICLE

ÂQRS	SYSTOLIC PRESSURE IN RIGHT VENTRICLE (AVERAGE)
$-65°$ to $-130°$	28.0 mm. Hg
$0°$ to $+60°$	30.0 mm. Hg
$+75°$ to $+135°$	44.5 mm. Hg
$+150°$ to $+170°$	48.0 mm. Hg

Based on these concepts, the shunt flow per cent was determined in 41 of our cases, and we tried to establish a correlation between the shunt flow and the electrocardiogram. Fig. 3 shows the correlation between the shunt flow per cent and the ÂQRS. As one can see, with the increasing amount of the shunt a greater deviation of the ÂQRS towards $\pm 180°$ is noted.

The correlation between the shunt flow per cent and the localization of the QRS vector in the frontal plane in our series is comparable with the findings of Walker[5] on the relationship between the mean ventricular axis and the amount of the pulmonary flow. Such was to be expected, since the amount of pulmonary flow certainly depends on the magnitude of the shunt flow through the interatrial septal defect.

T Axis.—The T axis was determined in 41 of our 44 patients. It was localized between 0° and +60° in 31 cases, or in 75.6 per cent; between +75° and

TABLE II. CORRELATION BETWEEN P WAVES IN V_1 AND V_2 AND MAGNITUDE OF SHUNT FLOW

SHUNT FLOW %	TALL PEAKED P WAVES IN V_1	TALL PEAKED P WAVES IN V_2
Below 40	0%	11.1%
Between 40 and 70	5.5%	55.5%
Above 70	69.2%	100%

$-170°$ in 6 cases, 14.6 per cent; and markedly deviated to the left (between $-15°$ and $-60°$) in 4 cases, 9.7 per cent. It was not possible to establish a correlation between the ÂT, the systolic right ventricular pressures, and the magnitude of the shunt flow. In the great majority of cases in which there was marked deviation of the ÂT, either to the right or to the left, this probably occurred on account of a digitalis effect, because other signs suggestive of the action of digitalis on the electrocardiogram, as for instance, S-T segment changes and shortness of the Q-T_c, were found.

P Wave.—The duration of the P wave in 38 cases was equal to or less than 0.10 second, and in 6 cases it was more than 0.10 second. In an attempt to establish a correlation between the P-wave pattern in right precordial leads, the pressures in the right auricle, and the magnitude of shunt flow, it was found (1) that there is no definite correlation between P waves in V_1 and V_2 and the pressures in the right auricular chamber; and (2) that in 9 cases in which the shunt flow was low, that is, below 40 per cent, only 1 showed tall peaked P waves in V_2. (See Figs 4, 5, 6.) The more the magnitude of shunt flow, the more peaked became the P waves in V_2. As the degree of this shunt increased, then there also appeared peaked P waves in V_1. Table II illustrates this correlation.

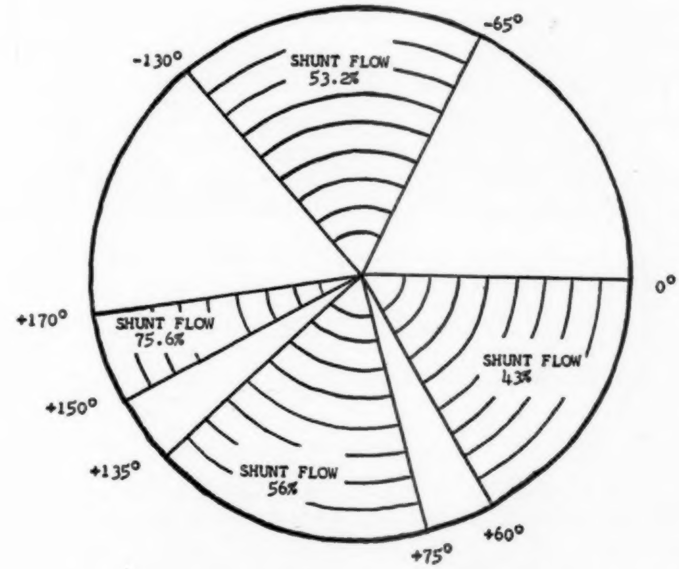


Fig. 3.—Correlation between the average of shunt flow per cent and ÂQRS in 44 cases of interatrial septal defect.

P-R Interval.—The P-R interval varied between 0.12 and 0.27 second, with the average being 0.165 second. In 29 cases it was shorter than 0.18 second; in 12 cases it was between 0.18 and 0.20 second; in 3 it was increased above 0.20 second.

Ziegler[7] is in agreement with our concept that enlarged P-R intervals, as far as interatrial septal defects are concerned, appear only in very large defects, or in those with special localization so as to affect the A-V conduction.

In our series there were no cases of arrhythmia, except in one patient who had in the same electrocardiogram a pacemaker shifting from the sinoauricular node to the atrioventricular node.

It was of interest that we found not one case of atrial fibrillation in our series, in spite of the obvious right auricular distention present in a large number of these patients. Walker[5] has also emphasized the absence of atrial fibrillation in his series. In the study of auricular physiopathology this would seem to be of much interest since this type of arrhythmia is found in a great number of cases of left auricular dilatation. It would appear that the right and left auricle behave differently under loading factors.

QRS Complex.—The duration of the QRS complex varied between 0.055 and 0.11 second. In our series there were no cases of the so-called "complete right bundle branch block."

In studying this QRS complex we tried to appreciate its morphology in V_1 and to correlate this data with the localization of the mean ventricular axis in the frontal plane, the pressures in the right ventricle, and the magnitude of shunt flow through the defect. Table III summarizes the findings covering the QRS complex pattern in V_1. As one sees in this table, a late R wave (R′) was present in this lead in 34 cases, or 77.2 per cent, and was absent in 10 cases, or 22.8 per cent. In 9 cases, 20.4 per cent, there was an initial R, which was followed by an S wave in 6 of these cases; in 3 this S wave was absent. In 1 patient we found the normal rS pattern. In this case the pressures were normal in the right ventricle (22/−2 mm. Hg). As is shown in Table IV, 3 cases of this group had marked

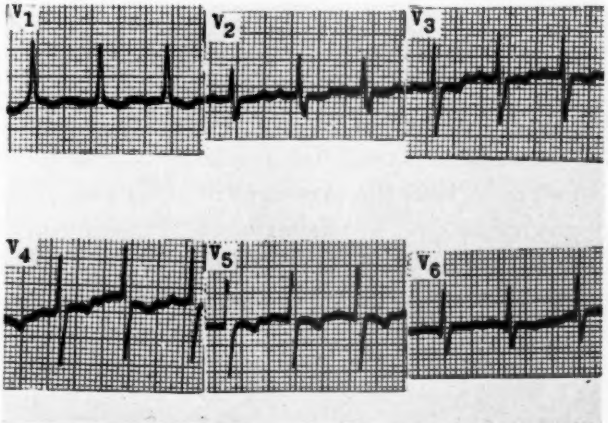
TABLE III. SUMMARY OF THE QRS PATTERN IN V_1 IN 44 PATIENTS WITH ATRIAL SEPTAL DEFECT

	MORPHOLOGY OF QRS COMPLEX IN V_1							
	QR	QRS	rsR′	rsr′	rsR′s′	RS	R	rS
Number of Cases	1	1	17	1	14	6	3	1

TABLE IV. CORRELATION BETWEEN THE AMPLITUDE OF THE R WAVE AND THE PRESSURES IN THE RIGHT VENTRICLE IN 9 CASES OF INTERATRIAL SEPTAL DEFECT

CASE	AMPLITUDE OF THE R IN V_1 (MM.)	PRESSURES IN THE RIGHT VENTRICLE (MM. Hg)
1.	11	80/4
2.	8	98/10
3.	8.5	38/3
4.	6.8	42/0
5.	7	40/3
6.	20	114/16
7.	9	22/4
8.	13	25/0
9.	7	20/3

Fig. 4.



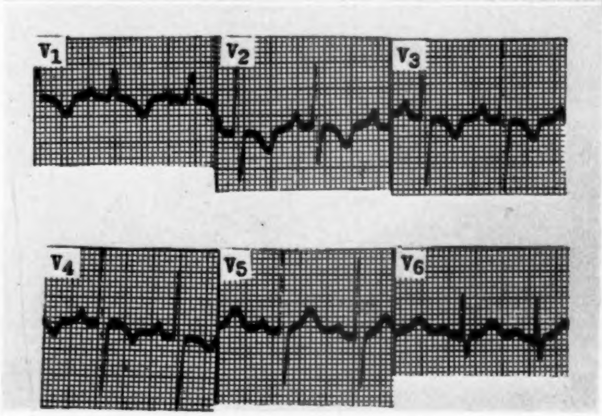


Fig. 5.

Fig. 4.—Shows the small P waves in V_1 and V_2 in a case of atrial septal defect with a shunt flow of 25 per cent. No R′ in V_1.

Fig. 5.—Peaked and tall P waves in V_2 in a case of atrial septal defect with a shunt flow of 65.6 per cent. The amplitude of R′ in V_1 is 4.5 mm. Hg.

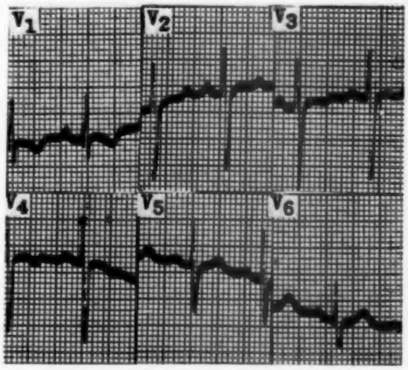


Fig. 6.—Peaked and tall P waves in V_1 and V_2 in a case of interatrial septal defect with a shunt flow of 93.4 per cent.

hypertension of the lesser circulation; in 3 others this hypertension was moderate in degree, and in 3 patients the pressures were within normal limits. It is of interest to point out that the patient with the tallest R wave in V_1 and the highest systolic pressure in the right ventricular chamber had also an associated interventricular septal defect. On account of the small number of cases in this group of R or RS pattern we could not establish a definite correlation between the amplitude of the R wave in V_1 and the pressures in the right ventricle. However, it is important to emphasize that in our series of 34 cases in which the R or RS pattern was not found, in only 1 was there an increase in right ventricular pressure (73/−2 mm. Hg). In this patient, however, there was associated pulmonic

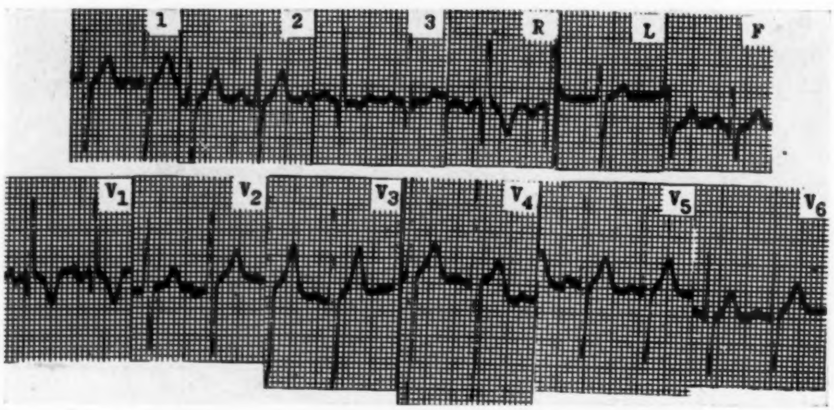


Fig. 7.—The RSR′ pattern in V_1 in a patient with interatrial septal defect and associated pulmonic stenosis and anomalous pulmonary venous drainage. In this case the pressure in the right ventricle was 73/−2 mm. Hg.

stenosis and anomalous pulmonary venous drainage (Fig. 7). We may so conclude from our experience that in the absence of R or RS pattern in V_1, as far as interatrial defects are concerned, a marked hypertension in the right ventricle is not expected. However, this morphology can appear either in the presence or in the absence of marked systolic pressure in the right ventricular chamber.

We tried to establish a correlation between the magnitude of the shunt flow and the QRS complex morphology in Lead V_1. In those cases in which the shunt flow was below 30 per cent we did not find a single one presenting a late R wave (R′) in this lead. The more the magnitude of shunt flow increased, the more

TABLE V. CORRELATION BETWEEN THE MAGNITUDE OF THE SHUNT FLOW AND THE R′ IN V_1

SHUNT FLOW %	R′ IN V_1
Below 35	Absent
Between 35 and 80	Amplitude (average) 4.4 mm.
Above 80	Amplitude (average) 11.5 mm.

the pattern of RSR′ was found. In the cases with very large shunt flows, the height of the R′ wave increased proportionally (Figs 4, 5, 8). Table V shows the relationship between the average of the R′ amplitude in Lead V_1 and the magnitude of shunt flow. The conclusions concerning this correlation will be stressed later. In only 1 case in this series was the flow of the reversed type, that is from right to left.

No correlations could be made among the patient's age, the magnitude of shunt flow, and the pressures in the right ventricle.

ECG Changes After Surgery.—Table VI summarizes the electrocardiographic changes in 12 patients after open heart surgery. All postoperative records were done within a period of 8 to 40 days following surgery.

TABLE VI. ECG CHANGES FOLLOWING SURGERY

CASES	SAP		SÂQRS		QRS IN V_1 (MEASUREMENT OF VALUES IN MM.)	
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER
1.	+60° F*	+30° B	+135° B	+125° ∥	R = 2.2 S = 0.5 R′ = 8.5 S′ = 2.5	R = 1.5 S = 3.5 R′ = 8 No S′
2.	+50° F	+ 0° B	+125° F	+110° F	R = 1.5 S = 0.1 R′ = 5.2 S = 0.5	R = 1 S = 1.5 R′ = 3 No S′
3.	+15° F	−35° B	+135° ∥	+135° F	R = 18 S = 4	R = 14 No S
4.	+55° F	+60° ∥	+ 60° B	+ 25° B	R = 2.2 S = 0.1 R′ = 4 S′ = 8.5	R = 1 S = 1 R′ = 4 S′ = 0.5
5.	+30° B†	+25° B	+160° F	+120° F	R = 0.3 S = 2.5 R′ = 10.5	R = 0.1 S = 3 R′ = 8
6.	+40° F	+35° B	+100° B	+ 85° B	R = 0.1 S = 0.2 R′ = 2 S′ = 2	R = 0.5 S = 2 No R′ No S′
7.	+45° ∥‡	+45° B	+110° F	+100° F	R = 0.5 S = 4 R′ = 5.5	R = 0.5 S = 3 R′ = 4.5
8.	+70° F	+60° ∥	+170° F	+130° B	R = 1.5 S = 1 R′ = 14 S′ = 1	R = 2 S = 6 R′ = 5 No S′
9.	+45° B	+40° ∥	+ 80° ∥	+ 75° ∥	R = 2.5 S = 1.2 R′ = 1 S′ = 1	R = 3.3 S = 0.3 R′ = 0.8 S′ = 1
10.	+30° F	+30° ∥	+130° ∥	+125° F	R = 1 S = 1.2 R′ = 9 S′ = 5	R = 17 No S No R′ No S′
11.	+60° F	+65° ∥	+ 95° B	+ 95° B	R = 1 S = 1.5 R′ = 5	R = 2.2 S = 7 No R′
12.	+25° F	+10° ∥	+110° F	+100° F	R = 2.5 S = 4 R′ = 7.5	R = 2 S = 4 R′ = 6

*The spatial vector is pointing forward.
†The spatial vector is pointing backward.
‡The spatial vector is parallel to the frontal plane.

In 8 cases, or 66.6 per cent, there was a tendency of the vector of auricular activation to deviate to the left in the frontal plane, and in 10 cases, or 83.3 per cent, to deviate backward in the horizontal plane. These changes in the SAP are, in our opinion, a good index of the correction of the septal defect, since they show a relative predominance of the left auricle over the right auricle after the surgical procedure. Such predominance was to be expected since the left auricular chamber no longer has a low-resistance pathway for flow, and the right auricle is no longer overloaded by the shunt.

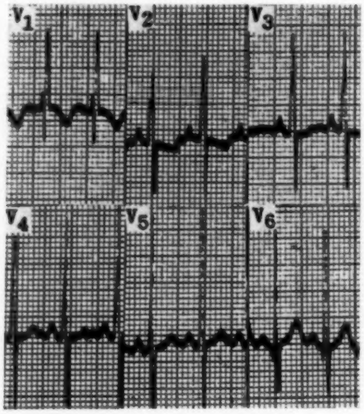


Fig. 8.—A case of interatrial septal defect with a large shunt flow (84.9 per cent). The R′ in V_1 measures 14.5 mm. in height.

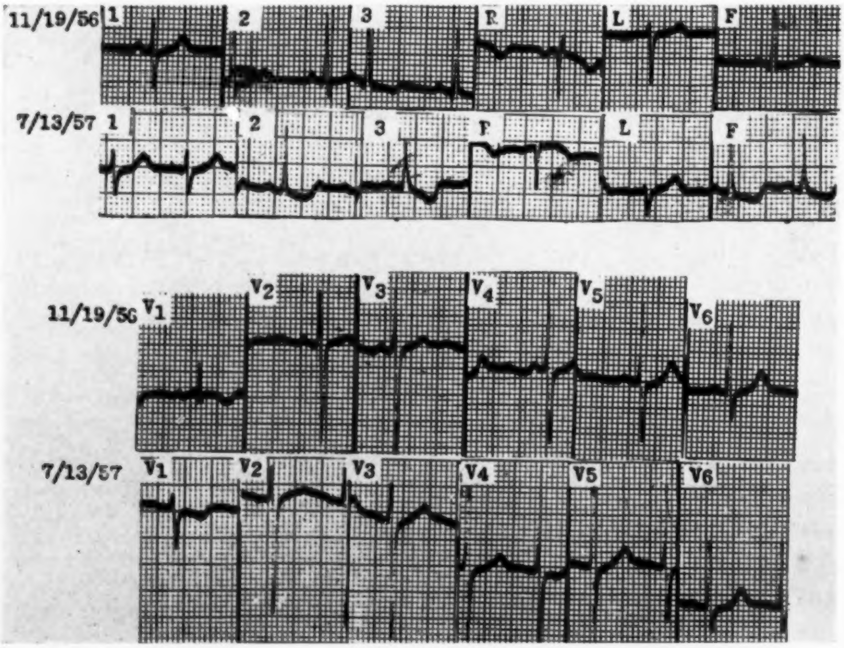


Fig. 9.—Shows the electrocardiographic changes after closure of the atrial septal defect. Note the disappearance of the RSR′S′ pattern in V_1 after surgery.

The mean axis of ventricular activation showed in 10 cases (83.3 per cent) a lesser deviation to the right in the frontal plane when compared with the localization before surgery. The lessening of the deviation to the right of the ventricular vector may correspond to a diminution of the dilatation of the right ventricle, as a consequence of a decreasing overloading in this chamber. As regards the ÂQRS in the horizontal plane, we found no changes following operation.

The changes in the QRS in Lead V_1 are of particular interest. As one can see, in 11 cases there was a late R wave (R′) before operation. In 9 patients this wave showed more or less of a decrease in its voltage, and in 2 cases the R′ disappeared completely. In 7 cases there was a late S wave (S′). In 5 cases this S′ wave completely disappeared, in 1 its voltage decreased, and in 1 it remained the same after surgery (Fig. 9). These changes in R′ and S′ will be discussed later. In 1 case an RS pattern was found before surgery, and after operation the R decreased in voltage and the S disappeared. We could find no explanation for this.

DISCUSSION

It was emphasized in the beginning of this paper that the classical RSR′ pattern in Lead V_1 did not mean a block in the right bundle branch itself as far as interatrial septal defect was concerned. If such a block really existed, how could we explain the changes in this pattern after surgery? How could one justify the disappearance or decrease in amplitude of the R′ or S′ after the closure of the septal defect? Would it be possible for a block in the right branch of the bundle of His to disappear on account of an interauricular surgical maneuver? Furthermore, how could we explain the substitution of the RSR′ by an R or RS pattern in cases in which pulmonary hypertension develops? We are not the first to discuss this problem. Walker[5] in an interesting analysis has also pointed out some of these facts. Peñaloza and Tranchesi[8] in one study about ventricular activation described the R′ wave as representing the vector of the depolarization of the basal portions of both ventricles and of the high parts of the interventricular septum. Intracavitary studies of Sodi-Pallares,[9] Kossman,[10] and other authors also lead to the same conclusion. Investigations of Kjellberg[11] showed that in interatrial septal defects there is a predominant hypertrophy of the crista supraventricularis and dilatation of the right ventricular chamber at this level.

The possibility of the R′ representing activation of this region has already been considered. It is also important to emphasize the frequency with which a late S wave (S′) appears in Lead V_1 in atrial septal defect and the frequency with which this wave decreases in amplitude or disappears after closure of the septal defect. Our studies on electrocardiographic changes following open heart surgery in patients with interventricular septal defect and infundibular pulmonic stenosis show that the S′ wave probably represents delayed conduction through the higher parts of the interventricular septum.[12] All the foregoing studies point out that the RSR′ or RSR′S′ pattern in right precordial leads means anatomic changes in the basal regions of the right ventricle and the higher parts of the interventricular

septum. The reasons for the preference of these changes in such regions, in interatrial septal defects, are not yet perfectly established. However, some considerations based on the hemodynamics of the heart and on the anatomy of the conduction system can be discussed. After the studies of Rushmer and associates[13] upon the mechanism of right ventricular contraction, it has been established that this contraction is effected primarily by shortening of the ventricle along its longitudinal axis, with no significant changes in the width of the ventricular cavity. The muscles of the basal region, possibly on account of their situation (outflow tract), seem to bear the major burden created by the excessive blood volume, which certainly brings about dilatation and hypertrophy in this region. Sodi-Pallares[14] and Prinzmetal[15] showed that in the basal portions of both ventricles, on account of the diminutive number of fibers of Purkinje as compared with other regions of the heart, the wave of depolarization travels more slowly. Such phenomenon will facilitate in a special way a delay in conduction of these parts when dilated and/or hypertrophied. As soon as pulmonary hypertension develops, these regions will not be able to cope with the hemodynamic burden, and so the whole right ventricle will hypertrophy in order to overcome the increased pulmonary arteriole resistance (concentric right ventricular hypertrophy). As a consequence of this generalized hypertrophy there is no longer a predominance of the basal regions, so that the electrocardiographic pattern of concentric hypertrophy is superimposed, giving rise to the R or RS morphology. The correlation obtained in our series between the QRS pattern in V_1 and the shunt flow seems to agree with these facts. The observation that with increasing magnitude of shunt the R′ wave becomes taller would suggest that the increased overloading during ventricular diastole gives rise to greater distention of the basal regions of this chamber, thus causing more marked delay in conduction time. In cases without pulmonary hypertension the magnitude of the shunt maintains a relationship with the size of the septal defect, if we admit that the larger the defect the larger is the volume of blood which passes from the left to the right atrium. When the pressures in the pulmonary artery and in the right chambers increase, we can no longer take the magnitude of the shunt as an index of the size of the defect. The increase in pressure in the right atrium offers a resistance to the left-to-right shunt in such a way that even in the presence of large defects, the gradient of pressure between the auricles being very small, the shunt decreases considerably. In some cases, as in one of our patients, the pressures in the right atrium are higher than in the left, and the shunt is reversed.

Concerning the terminology "diastolic overloading" used by Cabrera and Monroy[3] for the RSR′ pattern in the right precordial leads, it is our opinion that it does not mean diastolic overloading itself, but, as we have emphasized, delay in activation in the basal portions, which can be seen also in other congenital anomalies, such as pulmonic stenosis, to which the terminology "diastolic overloading" cannot be applied. We must stress, however, that in the majority of cases the dilatation and hypertrophy of the basal regions of the right ventricle and of the interventricular septum appear in those anomalies that bring to the right ventricle an overloading of the diastolic type, because of the hemodynamic changes we have already discussed.

The correlation obtained in our patients between the morphology of the P waves in the right precordial leads and the magnitude of the shunt flow lead us to the conclusion that tall peaked auricular waves in V_1 and V_2 have some relationship with the degree of overloading imposed on the right auricle by the septal defect. As we have shown, in the group in which the shunt flow was very large, the incidence of peaked P waves increased not only in V_2 but also in V_1. We hope to be able soon to establish more definite results on this subject, with intracavitary potentials and vectorcardiographic studies.

We could not secure any correlation between shunt flow and intracavitary pressures, which corroborates the opinion that atrial septal defect does not lead in itself to a generalized hypertrophy of the right ventricle. However, we did find some relationship between the magnitude of the shunt flow and the degree of ÂQRS deviation to the right. If we acknowledge that the deviation of the mean ventricular axis is a good index to correlate with the dilatation of the ventricular chambers, such a fact emphasizes the well-known hemodynamic concepts which show a direct relationship between the volume of blood and the degree of dilatation.

CONCLUSIONS

1. RSR′ or RSR′S′ pattern in Lead V_1, as far as interatrial septal defect is concerned, does not mean disturbance in conduction of the right branch of the bundle of His itself, but delay in activation of the basal portions of the right ventricle and of the higher parts of the interventricular septum.
2. This delay in conduction is due to hypertrophy and dilatation of the regions mentioned above.
3. Although the morphology of RSR′ or RSR′S′ is not an obligatory sign of diastolic overloading of the right ventricle, it appears mostly in those anomalies that produce such type of overloading.
4. In uncomplicated interatrial septal defect the fundamental hemodynamic change is an increase in blood volume-work without significant increase in pressure in the right ventricular chamber.
5. In our opinion there is a definite correlation between the morphology of the QRS complex in V_1 and the magnitude of the shunt flow.
6. In the same way, the morphology of the P wave in the right precordial leads bears some relationship with the magnitude of this flow.

SUMMARY

The authors have presented an electrocardiographic study in 44 patients with interatrial septal defects and established a correlation with the hemodynamic data. Changes in the electrocardiogram after the closure of the defect under direct vision are considered. Emphasis has been made of the authors' opinion concerning the meaning of the RSR′ or RSR′S′ pattern, and they have established a comparison between this morphology and the magnitude of the shunt flow through the septal defect. In the same way, a comparative study between the P wave pattern in the right precordial leads and the shunt flow was made.

The authors are indebted to M. P. Sambhi, M.D., Helen Kleinhenz, R.N., and Marjorie McIntyre, R.N., who aided in this study.

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On the Mechanism of Production of the Heart Sounds

A. A. Luisada, M.D., C. K. Liu, M.D., C. Aravanis, M.D., M. Testelli, M.D., and J. Morris, B.A., Chicago, Ill.

Graphic tracings of the heart sounds (phonocardiograms) have been recorded for over 50 years. Physicians and physiologists gradually became accustomed to certain typical vibrations which could be recognized within the groups of "noises" that form the sounds. However, different interpretations were attached to these vibrations, and even now there is no agreement about their meaning. As the "reading" of a clinical phonocardiogram is based on the interpretation of the normal tracing, knowledge of the latter is essential.

THE CHARACTERISTICS OF THE HEART SOUNDS

As known, the first sound is made of a prolonged series of vibrations. Caeiro and Orias,[1] and Orias and Braun Menendez[2] recognized that it is often made of two separate groups of vibrations. They thought that the first group corresponded to the isometric contraction; the second, to the ejection phase of ventricular systole. Rappaport and Sprague[3] also recorded in some cases two larger vibrations within the central phase of the first sound. Their interpretation was similar to that of the previous authors. Luisada, Mendoza, and Alimurung,[4] for practical purposes, divided the first sound into three phases: initial, lower-pitched vibrations; central, higher-pitched vibrations; and final, lower-pitched vibrations.* They attributed the central, most important, phase to valvular events. They further recognized two groups of larger vibrations within this central phase and attributed the first to closure of the A-V valves; the second, to opening of the semilunar valves. Simultaneous recording of carotid tracings confirmed this interpretation. Subsequently, Luisada, Alimurung and Lewis[8] made a series of studies in rabbits and dogs. They came to the conclusion that "sudden changes in muscular tension activate, first the A-V valves, and then the semilunar valves. This rapid succession causes a double vibration of the cardiac wall and is further transmitted to the chest wall including high-pitched (sound tracing) and low-

From the Division of Cardiology of the Chicago Medical School at Mount Sinai Hospital, Chicago, Ill.

This study was made under the tenure of a Teaching Grant of the National Heart Institute, U.S. P.H.S., and was aided by Research Grant H-3416 of the National Heart Institute.

Received for publication Sept. 17, 1957.

*This division is similar to that suggested by Battaerd[5] and accepted by Wiggers and Dean[6] and Hess.[7]

pitched (cardiogram) components. Although simultaneous with the action of the valves, these vibrations are likely to arise in both the valvular and the muscular structures as a response to rapid changes in tension and pressure." Subsequently, Leatham[9] postulated that the first large vibration was due to closure of the mitral valve; the second, to closure of the tricuspid valve. As proof of this, he mentioned (1) that the second group of vibrations is larger over the tricuspid area, and (2) that it follows the rise of pressure in the aorta (carotid tracings recorded). Point 1 fails to have value because the "tricuspid area" corresponds to a central point which is equally distant from the anatomic projections of both the aortic and the tricuspid valves. Point 2 is not confirmed by clinical tracings (Fig. 8,*C* and 10).

In regard to the second sound, it is generally agreed that it is due mainly to closure of the semilunar valves of both the aorta and pulmonary artery. Whenever these valves do not close at the same time, splitting of the sound occurs. Luisada, Mendoza and Alimurung[4] proved that, in normal subjects, a small low-pitched vibration may be recorded at the apex, due to the opening of the mitral valve. Furthermore, Leatham[9] showed that frequently two large vibrations can be found within the second sound and that the second represents the pulmonic component.

Characteristics of Apparatus Used For Phonocardiography.—The technical characteristics of the recording apparatus are largely responsible for the number and form of the observed vibrations. Therefore, a brief survey of the most important of them is necessary.

1. *Older systems based on the photographic recording of the vibrations of a membrane (Ohms' capsule, Frank's capsule, Wiggers-Dean capsule):* Standardization of the system was extremely difficult. The period of oscillation of the membrane created a "mechanical filter," so that only vibrations of certain frequencies were recorded while others were either modified or not recorded at all.

2. *Sanborn Stetho-Cardiette with "stethoscopic" microphone:* This system was based on a crystal (piezoelectric) microphone and an electronic system of amplification. It recorded with fidelity the lower frequencies between 20 and 60, but gradually decreased the amplification for higher frequencies. As a result, the lower frequencies were unduly magnified.

3. *Sanborn Twin-Beam with "stethoscopic" or "logarithmic" type of recording*: This system is based on a dynamic microphone and an electronic system of amplification. The lower frequencies are poorly recorded while those between 40 and 200 are greatly magnified in the "stethoscopic" system. In the "logarithmic" system the vibrations between 150 and 300 cycles per second are probably recorded best, while several disadvantages (excessive amplitude of the heart sounds, background "noise," etc.) prevent the recording of the high-pitched, small vibrations of certain murmurs.

4. *Selectively filtered phonocardiography:* Following the studies of Mannheimer,[14] selectively filtered phonocardiography was suggested by two of the authors with Richmond.[10] It was based on the use of a double band-pass filter and an additional D.C. amplifier. In spite of great advantages for clinical studies, this system was limited by the use of the phono amplifier of the Twin-Beam, which is poorly sensitive to low-pitched vibrations.

5. *New system:* A new system was made according to specifications* and is based on the use of (1) a Peiker piezoelectric microphone, sensitive to vibrations from 15 to 1,000 cycles per second; (2) an electronic system of amplification; (3) a low and high band-pass filter which attenuates at the rate of 12 decibels per octave; (4) a cathode-ray oscillograph projecting its light beams on sensitive bromide film running at speeds of 25, 50, or 100 millimeters per second.

*Built by "Electronics for Medicine" of White Plains, N.Y.

The basic and most significant frequencies of the sounds recorded with the new system (5) were the following: *Third and fourth sound*—they consist mainly of lower frequencies (15 to 50 cycles per second) with minimal overtones. *First sound*—the initial and final part are in the same range as the third and fourth sounds. The central part consists chiefly of relatively low frequencies (50 to 150 cycles per second), but there also are important overtones of shorter duration

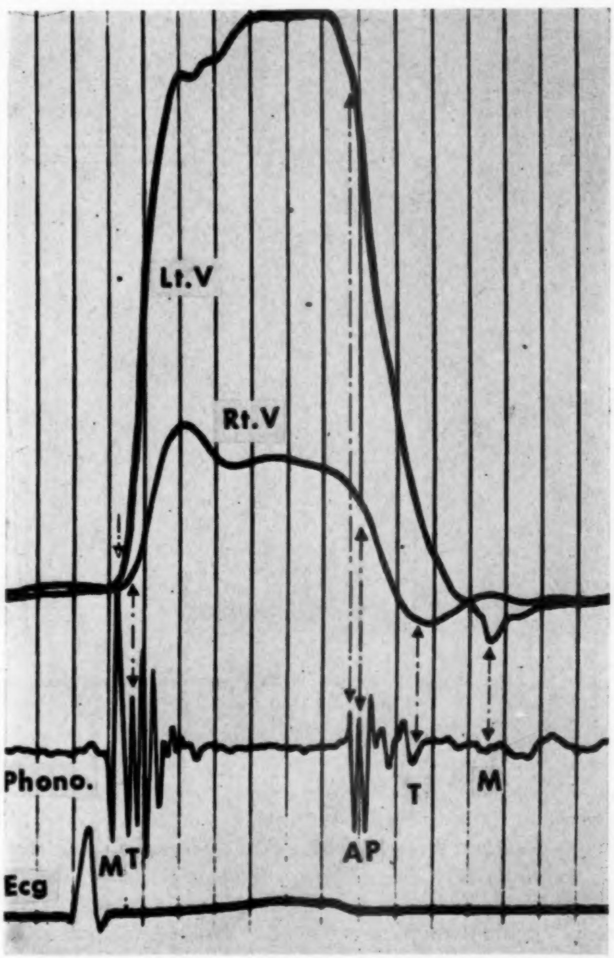

Fig. 1.—Dog. Right and left ventricular pressures. Phonocardiogram recorded at apex (band 60-110). ECG. Film speed = 100 mm./sec. Time lines = 0.04 sec.

in the frequency range of 200 to 400 cycles per second (Fig. 10). *Second sound*—the central part, including both the aortic and the pulmonic component, is made of medium frequencies (100 to 200 cycles per second). However, it also contains overtones of higher frequency (200 to 400 cycles per second) and magnitude, which are significant for recognition of the motions of the pulmonic and aortic valves.

MATERIAL AND METHOD

Our studies were made by using the recording microphone and apparatus mentioned above as the "new system." However, in some clinical tracings, use was made of a procedure similar to that outlined above under the term "selective phonocardiography,"[10] using the Twin-Beam and a Krohn-Hite filter. Two separate groups of studies were made.

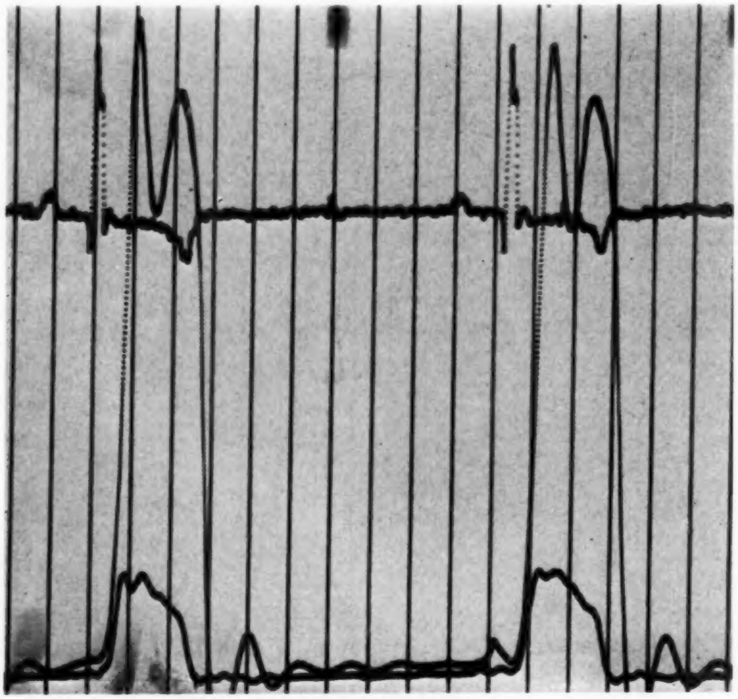

Fig. 2.—Dog. ECG. Right and left ventricular pressures. Film speed = 50 mm./sec. Time lines = 0.1 sec.

I. A study of heart sounds was made in 13 normal dogs. Nine of them were under morphine-chloralose anesthesia. Two had Nembutal anesthesia. Two had Nembutal plus hypothermia. The dogs were submitted to right and left heart catheterization: (1) right heart catheterization via a femoral or jugular vein (right atrium, right ventricle, or pulmonary artery), and (2) left heart catheterization via a femoral artery (left atrium, left ventricle, or aorta).

The catheters were connected with two Statham strain gauge P23D pressure recorders. The latter were carefully calibrated so that they gave the same response for the same change in pressure. The light beams of the cathode-ray recorder corresponding to the gauges were adjusted so that the zero lines were exactly superimposed. Simultaneous tracings of two equivalent chambers or vessels (right and left ventricle, aorta and pulmonary artery, etc.) were recorded at the same degree of amplification. In 5 dogs, two catheters were placed in the chambers of either the right or the left heart, so that simultaneous tracings of two chambers or vessels of the same side (right heart and pulmonary artery; left heart and aorta) were possible. In all the animal experiments the heart sounds were also recorded from one of the cardiac chambers (intracardiac phonocardiography) according to a method recently described by Luisada and Liu.[11] This method is based on differentiation, amplification, and filtration of the vibrations of higher frequency of the pressure gauge, followed by recording in the phono channel. Usually, intracardiac phonos were recorded in the band 60-110, occasionally in the band 60-250. In one experiment, two simultaneous intracardiac phonocardiograms were recorded, first from the two ventricles, then from the aorta and pulmonary artery.

An external phonocardiogram was recorded in all dogs simultaneously with the pressure tracings. The same microphone and system used for human beings were employed here. The microphone was placed at the apex.

II. A clinical study of human subjects was performed in 12 normal male persons between the ages of 18 and 36 years. The "shape," length, and number of vibrations of the first and second sounds were studied by simultaneous recording of other tracings: low-frequency tracing of the apex and epigastrium; carotid and jugular tracing; and electrocardiogram. In some cases, instead

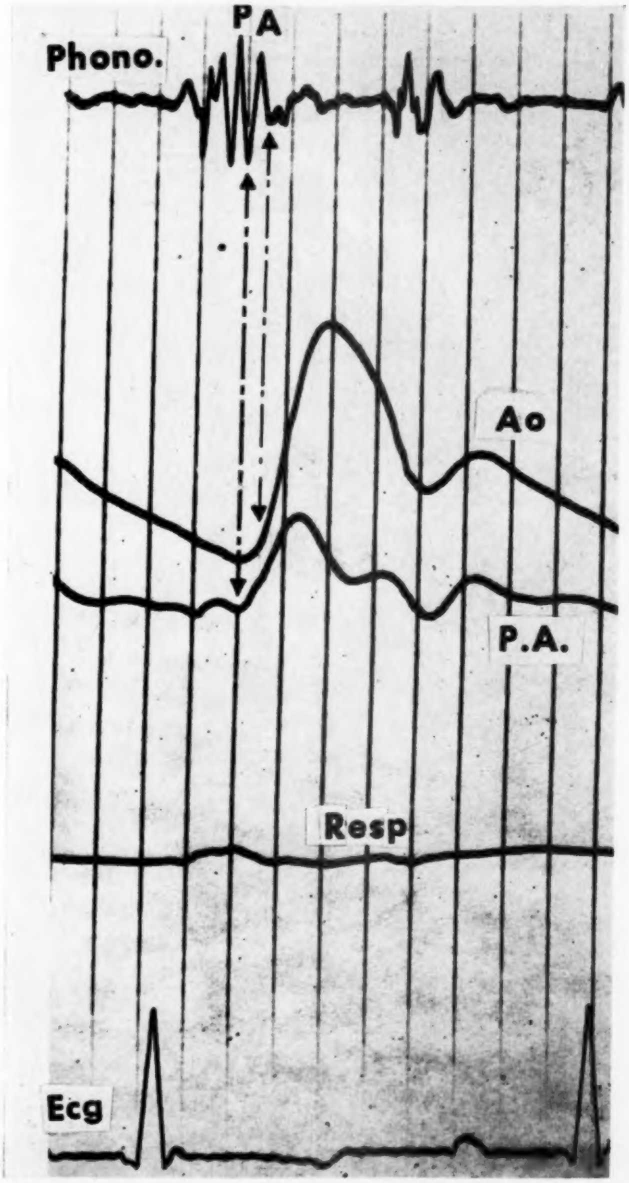

Fig. 3.—Dog. Phonocardiogram at apex (band 60-110). Aortic and pulmonic pressures (the aortic tracing has been shifted downward for better comparison). Respiratory tracing. ECG. Film speed = 100 mm./sec. Time lines = 0.04 sec.

of the carotid tracing, a tracing of the suprasternal notch was recorded. The latter tracing records the pulsation of the aortic arch, which has practically no delay over that of the ascending aorta. All pulse tracings were recorded with piezoelectric microphones which have the advantage of electric recording and no delay due to air transmission through long tubing.

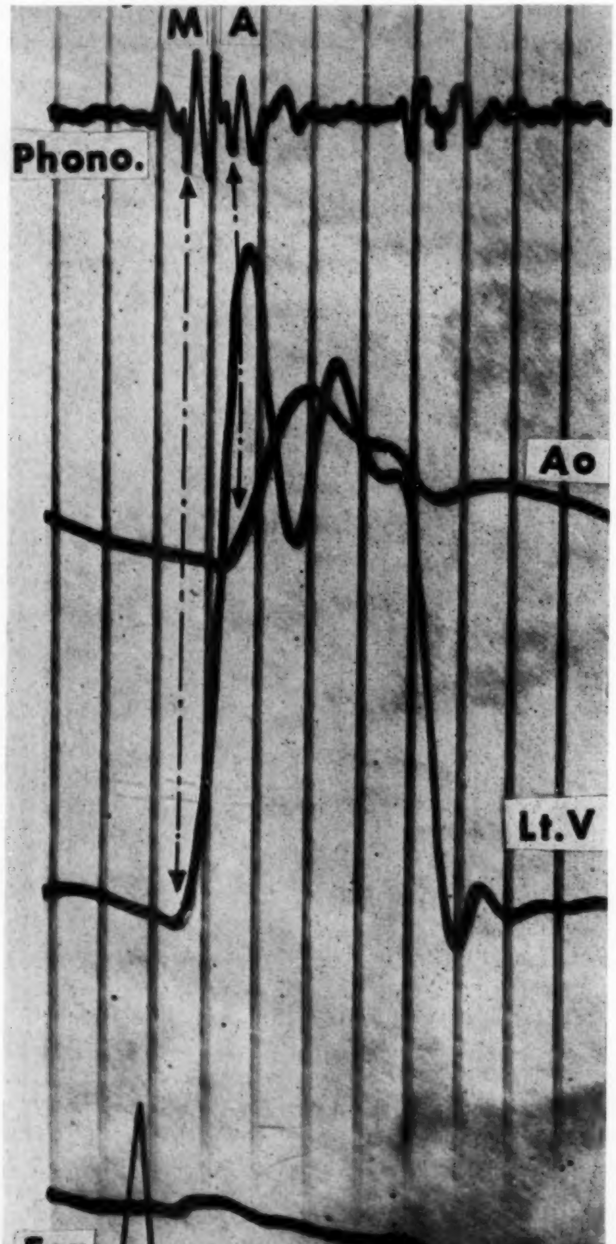

Fig. 4.—Dog. Phonocardiogram at apex (band 60-110). Pressures of aorta and left ventricle. Respiratory tracing. ECG. Film speed = 100 mm./sec. Time lines = 0.04 sec.

RESULTS

Tracings in Animals.—Dogs with only moderate depression induced by the anesthesia and with a cardiac rate between 70 and 90 present a consistent relationship between right and left ventricular pressures.

1. In certain of the cycles, left ventricular pressure rises first and increases at a faster rate. Right ventricular pressure lags behind by 0.01 to 0.02 second and rises more slowly. It is reasonable to suppose that, in these cycles, mitral closure precedes tricuspid closure by 0.01 to 0.02 second (Fig. 1). This is confirmed by evaluating the moment of closure of each atrioventricular

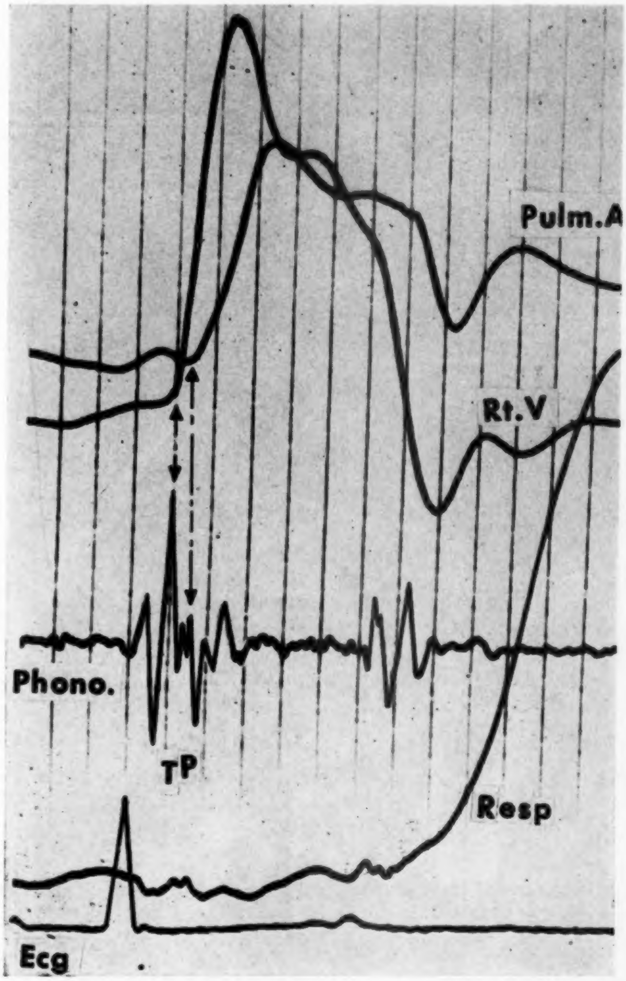

Fig. 5.—Dog. Pressures of pulmonary artery and right ventricle. Phonocardiogram at apex (band 60-110). Respiratory tracing. ECG. Film speed = 100 mm./sec. Time lines = 0.04 sec.

valve by the crossing of the atrial and ventricular tracings of each side. The closures of the mitral and tricuspid valves, occurring one after the other, coincide with two large vibrations of the phonocardiogram recorded at the apex in the band 60-110 cycles per second (Fig. 1). These vibrations are both in the first part of the central phase of first sound. In other cycles, the two pressures rise simultaneously, the difference being shown often by two subsequent cycles (Fig. 2). It is

likely that, in these cycles, the closure of the mitral and tricuspid valves is about simultaneous. The difference between cycle and cycle seems to be due to respiration which changes the amount of filling of the two ventricles.

2. The rise of pressure in the pulmonary artery always precedes that in the aorta. However, the interval between the two, which is usually in the range of 0.02 second, may become longer or shorter on account of different variations of pressure in the vessels, connected with respiration.

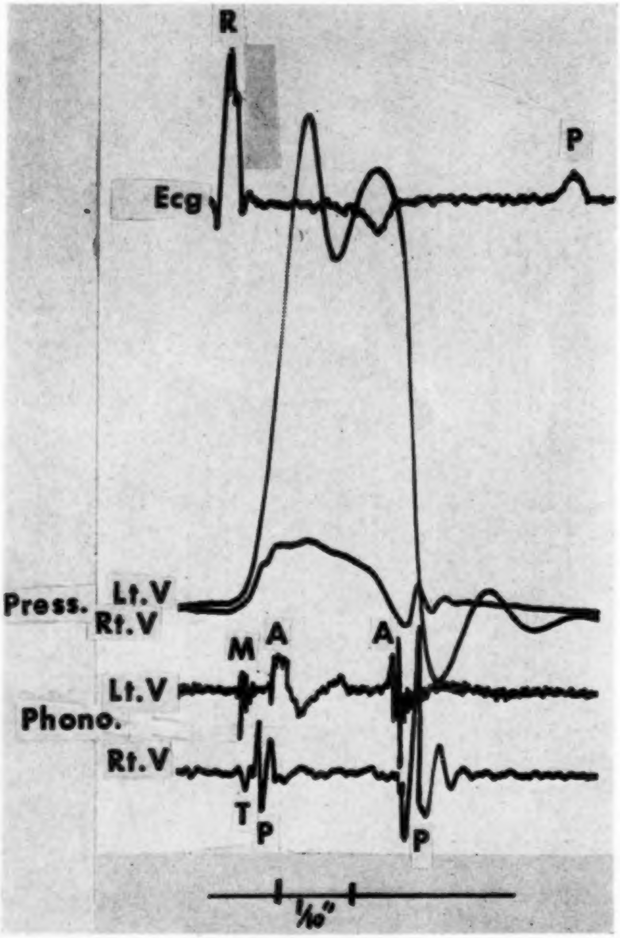

Fig. 6.—Dog. ECG. Pressures of right and left ventricles. Intracardiac phonocardiograms of same chambers. Film speed = 100 mm./sec.

These rises of pressure in the main vessels coincide with vibrations of the second part of the central phase of the first sound, as recorded at the apex (Fig. 3). It is reasonable to suppose that the vibrations created in the heart and large vessels by the opening of the semilunar valves are responsible for these vibrations.

3. The relationship of mitral closure versus aortic opening, and of tricuspid closure versus pulmonic opening, is also illustrated by Figs. 4 and 5. Fig. 4 shows the relationship of the left ventricular pressure tracing with that of the aorta. Fig. 5 shows the relationship of the right ventricular pressure tracing with that of the pulmonary artery.

4. The end of left ventricular systole always precedes that of the right. The beginning of the drop of the curve for each ventricle coincides with a separate vibration within the second sound.

Thus, normally the pulmonic component of this sound follows the aortic, with an interval of about 0.02 second (Figs. 1, 3, and 6).

5. The opening of the mitral valve always follows that of the tricuspid valve. Sometimes the interval between the two reaches 0.08 second (Fig. 1), while usually it is in the range of 0.04 to 0.06 second.

6. Rapid filling of the left ventricle always follows that of the right. The interval between the fillings of the two ventricles is similar to that between the openings of the respective A-V valves. For each ventricle the peak of rapid filling follows the opening of the respective A-V valve by 0.08 to 0.10 second; and the closure of the respective semilunar valve by 0.12 to 0.18 second.

7. For further confirmation of the above data intracardiac and simultaneous phonocardiograms of the two ventricles or of the aorta and pulmonary artery were recorded. Each intraventricular sound tracing reveals the closure of its A-V valve with a single vibration; subsequently, it shows (Fig. 7) both the opening of the respective semilunar valve (end of first sound) and the closure of the same valve (second sound).

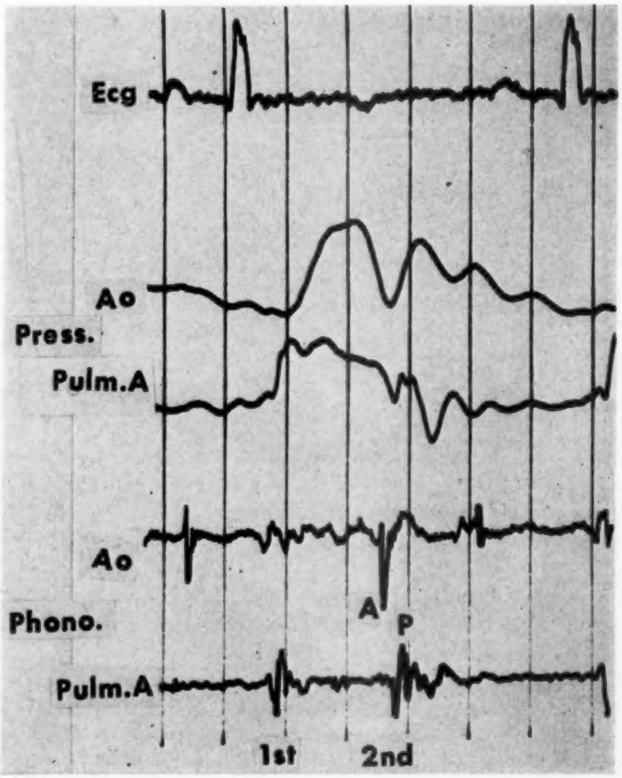

Fig. 7.—Dog. ECG. Pressures of aorta and pulmonary artery. Intravascular phonocardiograms of same vessels. Film speed = 100 mm./sec. Time lines = 0.1 sec.

As a result of the above measurements, a definite sequence of events can be ascertained for the dog (Table I, and Fig. 11).

Comparison of intracardiac tracings with external phonocardiograms reveals that the slow initial vibration which usually starts the sound at the apex precedes mitral closure. As this vibration is low pitched and is present in cases with atrial fibrillation, the only logical explanation is that it is caused by the tension of the ventricular mass prior to closure of the mitral valve.

TABLE I

SYMBOL	EVENT	INTERVAL IN SECONDS	HEART SOUND
	Q wave (ECG)		
		0.06–0.07	
M	Closure of mitral valve		
		0.00–0.02	
T	Closure of tricuspid valve		First Sound
		0.01–0.03	
P	Opening of pulmonic valve		
		0.01–0.02	
A	Opening of aortic valve		
A	Closure of aortic valve		
		0.02	
P	Closure of pulmonic valve		
		0.03–0.04	
OT	Opening of tricuspid valve		Second Sound
		0.04–0.08	
OM	Opening of mitral valve		
		0.00–0.04	
3R	Rapid filling of right ventricle		
		0.04–0.08	Third Sound
3L	Rapid filling of left ventricle		

Tracings in Human Subjects.—An interval which has acquired importance in the study of rheumatic patients with mitral valve lesions is the Q-1 interval. This should be measured between the beginning of Q and the first large vibration of the central phase of the first sound. Thus, any delay in mitral closure will be revealed by a prolongation of this interval. It is normally below 0.07 second.

As already ascertained in animals, the slow, small, initial vibration of the first sound preceding the central phase is probably due to tension of the ventricles, prior to closure of the mitral valve (Figs. 8,*C* and 10).

Tracings recorded with older methods showed, at times, multiple vibrations within the central phase of the first sound. However, the method employed in this study most consistently shows this phenomenon. The central phase of the first sound is made of several vibrations: frequently, 4 diphasic oscillations (Fig. 8), sometimes 5 or more. This is particularly true for tracings recorded at the apex, while tracings recorded at the epigastrium or at Erb's point usually show a shorter sound. The time intervals in men are similar to those in large dogs. The total duration of the central phase of the first sound was found to be between 0.08 and 0.10 second. The large vibrations which occur during this central phase have both lower and higher frequencies. The higher frequencies are often limited to two larger oscillations (Fig. 10), one of them at the beginning, the other toward the end of the phase. The last vibration precedes the rise of the carotid pulse and coincides with the rise of the aortic pulse (Figs. 8,*C* and 10). It also precedes the rise of pressure in the pulmonary artery (Fig. 9).

Following the central phase of the first sound there is a phase of lower-pitched and irregular vibrations. These follow the opening of the aortic valve and are inscribed during the ascending

branch of the carotid pulse, frequently lasting until the peak of the pulse wave (Figs. 8,*C* and 10). The most logical interpretation is that they represent vibrations caused by ejection of blood into the pulmonary artery and aorta.

In regard to the second sound, tracings recorded over the second left intercostal space frequently show a double vibration with a smaller (pulmonic) following a large (aortic) component

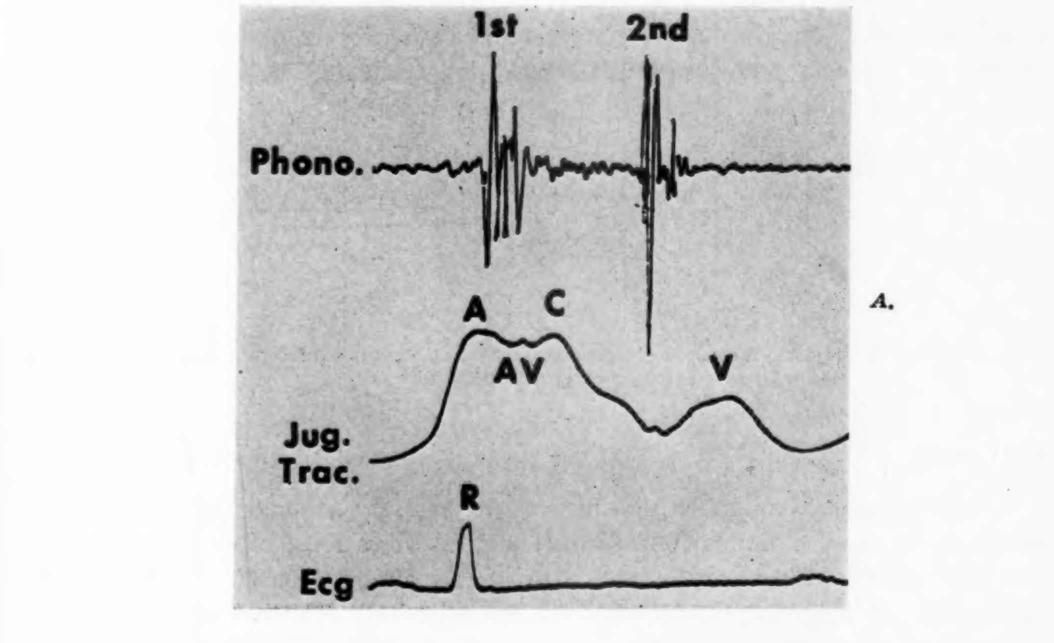

Fig. 8.—Phonocardiograms of three normal subjects recorded in the fourth left intercostal space. *A*, Compared with jugular tracing (*Jug. Trac.*). *B*, Compared with low-frequency tracing at apex or apex cardiogram (*Card.*). *C*, Compared with carotid tracing (*Carot. Trac.*).

(Figs. 8, *A* and 10). Simultaneous phonocardiograms reveal that the second sound at the apex is only, or mostly, aortic in origin. They also show that the last phase of the first sound may be of longer duration at the base than at the apex (Fig. 10). This is due to better transmission at the base of the late components, because of opening of the arterial valves and vascular phenomena.

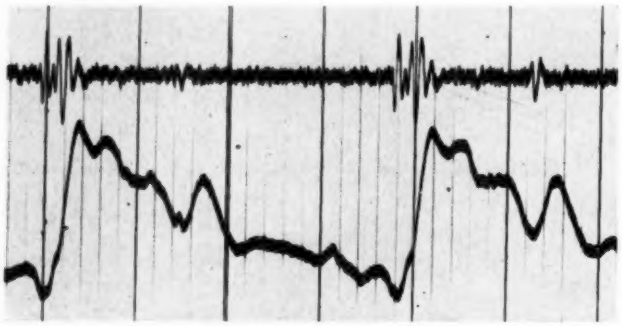

Fig. 9.—Normal subject. Stethoscopic phonocardiogram at third left intercostal space. Pressure tracing of pulmonary artery (24/9 mm. Hg).

DISCUSSION

Our research in animals and human subjects has proved that the central phase of the first sound is composed of several vibrations, often 4 in number, and that the best frequency band to record them is between 60 and 100 or 110 (with slow attenuation above and below those limits). These 4 vibrations have been identified as being caused by the successive play of the 4 cardiac valves in the following order: closure of mitral (M), closure of tricuspid (T), opening of pulmonic (P), opening of aortic (A). Filtered tracings in the range 200-400 may reveal only two vibrations.

Whenever two main groups of vibrations can be seen within this phase, they can be attributed to (1) closure of the A-V valves (MT) and (2) opening of the semilunar valves (PA). The statement that "tricuspid closure is responsible for the second group of vibrations" is disproved by the following considerations: (1) In large dogs, tricuspid closure (right ventricular pressure higher than right atrial) is either simultaneous with mitral closure (left ventricular pressure higher than left atrial) or follows the latter by 0.01 to 0.02 second. (2) The second group of vibrations of the central phase of the first sound coincides with the rise of the aortic or pulmonic pulse both in dogs and human beings. In dogs we have evidence that the rise of the pulmonic pulse precedes the rise of the aortic pulse and is simultaneous with the beginning of the second group of vibrations of the first sound. Since it is obvious that tricuspid valve closure occurs earlier than the opening of the pulmonic valve, the former cannot be responsible for vibrations occurring so late. Tracings recorded in man through right heart catheterization confirm this fact (Fig. 9). (3) The second group of vibrations of the central phase of the first sound is separated from the first group by an interval of 0.04 to 0.05 second. This is much too large to be explained by an asynchronism

between mitral and tricuspid closure. Even though often existing, such asynchronism is brief and does not exceed 0.02 second. (4) The initial phase of the first sound occurs prior to mitral closure and coincides with the initial phase of tension of the ventricular myocardium. The final phase of the first sound coincides with the expansion of the aorta and pulmonary artery, and their branches, and is obviously due to vascular vibrations.

The 4 components of the first sound had been described by Rodbard,[12] through recording on tape, but their causes, tentatively ascribed to valvular events, had not been definitely proved.

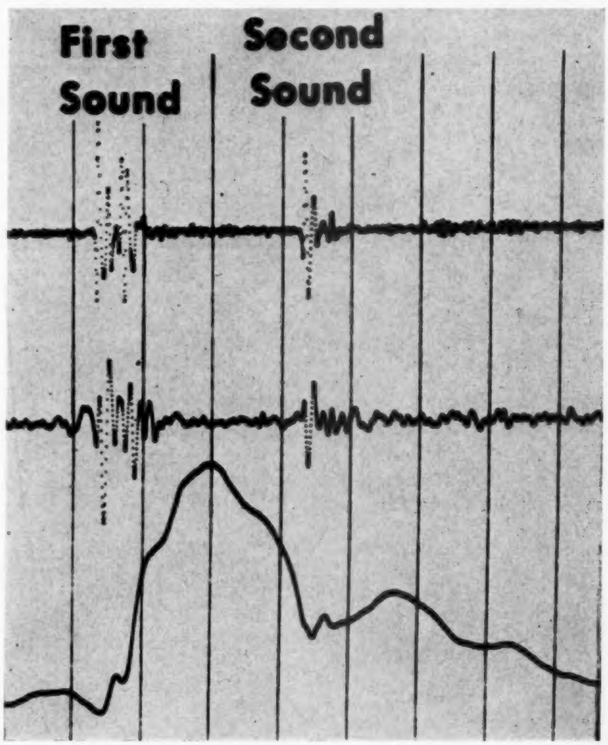

Fig. 10.—Normal subject. Upper tracing is high-frequency, filtered phonocardiogram at fourth left intercostal space (range 250-500). Middle tracing is medium-frequency, filtered phonocardiogram at same area (range 60-110). Lower record is pulse tracing at suprasternal notch (aortogram). The high-frequency vibration (and the upper peak of the medium-frequency one) corresponding to the second group of vibrations of first sound coincides with the initial rise of the aortic pulse (the rise of a previous step coincides with the mitral closure—between the two is the isometric contraction). Film speed = 100 mm./sec. Time lines = 0.1 sec.

Records in normal human subjects with selective phonocardiography yield a pattern which is similar to that recorded in dogs and which can be considered typical for the frequency band 60-110.

The second sound is typically formed by two valvular components which follow each other in this sequence: closure of aortic (A), closure of pulmonic (P). After this, there is the opening of the A-V valves which occurs in this sequence: opening of tricuspid (T), opening of mitral (M).

Animal experiments prove that rapid filling is usually asynchronous for the two ventricles, occurring in this sequence: rapid filling of right ventricle (3R), rapid filling of left ventricle (3L). The symbols 3R and 3L given to these phenomena are based on the fact that they often are the cause of a third sound.

This knowledge explains why, in cases with altered cardiac dynamics, one can observe *two* third sounds (Luisada[13]).

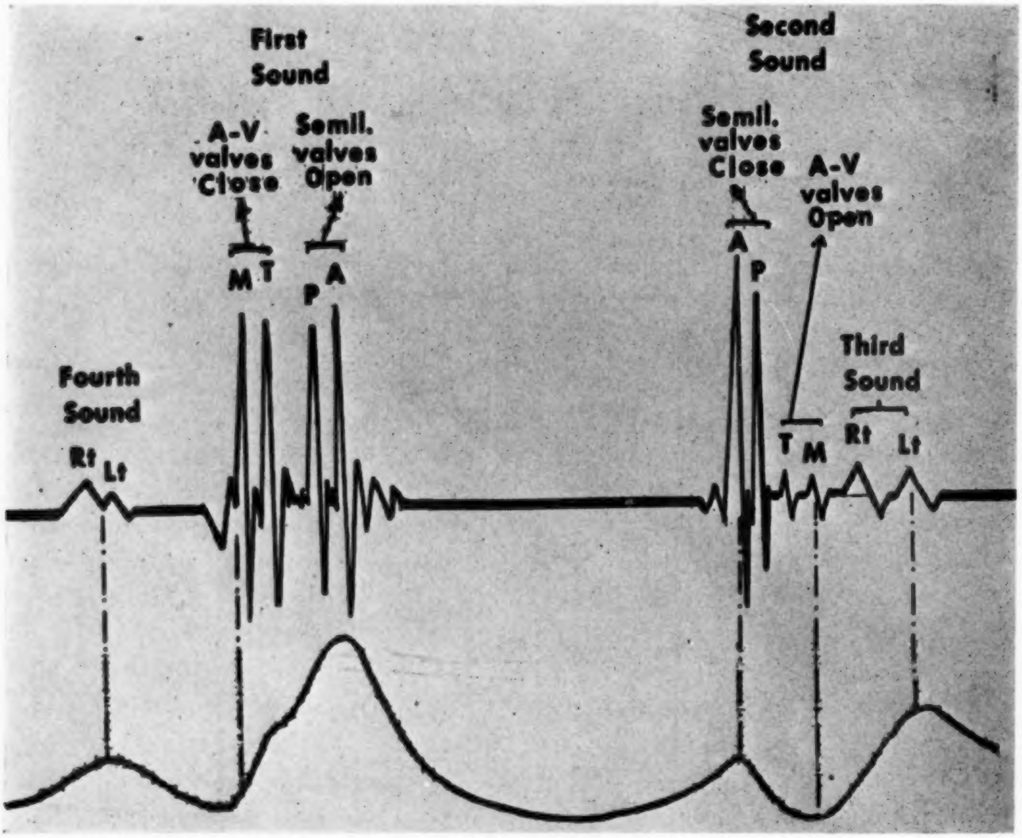

Fig. 11.—Scheme of a sound tracing. The meaning of the various components is indicated. Below is an apex cardiogram (low-frequency tracing).

SUMMARY

The mechanisms of the heart sounds have been investigated by means of animal experiments and the recording of tracings in normal human subjects.

Simultaneous tracings of pressure have been recorded in dogs from the two ventricles, from one ventricle and its respective atrium, and from the aorta and pulmonary artery. The time relationship of the motion of the various valves was revealed by these tracings plus simultaneous external phonocardiograms. Simultaneous intracardiac phonocardiograms confirmed these data.

Selective phonocardiograms have been recorded through various filters in man, together with low-frequency tracings of the precordium, carotid and aortic tracings, and jugular tracings. The following conclusions have been reached (Fig. 11):

1. The first sound is made of 3 phases: low-pitched beginning, due to myocardial tension; higher-pitched central phase, due to valvular events; low-pitched final phase, due to vascular phenomena. The central phase contains at least 4 vibrations which correspond to the motion of the 4 valves in the following order: mitral closure, tricuspid closure, pulmonic opening, aortic opening. Whenever one or more large vibrations correspond to the phase of ejection, they are likely to be of a vascular nature.

2. The second sound is made of 3 phases: low-pitched beginning, due to eddies preceding the valvular closure; higher-pitched central phase, due to closure of the semilunar valves; and low-pitched final phase, due to final vibrations plus opening of the A-V valves. The central and final phases correspond, first, to the closure of the semilunar valves and, then, to the opening of the A-V valves, in this order: aortic closure, pulmonic closure, tricuspid opening, mitral opening.

3. Rapid filling of the ventricles is usually nonsimultaneous, in this order: rapid filling of right ventricle, rapid filling of left ventricle.

These data confirm some interpretations of previous workers but exclude others.

Time intervals for the various phases are given for large dogs.

Measurements taken in phonocardiograms of normal persons, recorded with a technique which is identical to that used in dogs, indicate that similar figures can be used in man.

ADDENDUM

After this paper had been submitted for publication, an article by Reinhold and Rudhe, entitled "Relation of the First and Second Heart Sounds to Events in the Cardiac Cycle," appeared in the British Heart Journal.[15] Inasmuch as the authors report data which might be considered as contradicting our findings, a brief comment is indicated.

1. Reinhold and Rudhe's study is based on electrokymograms. These tracings may have a certain lag due to: (a) electrical setup including filters, (b) lag of the fluorescent screen, (c) delay in the motions of cardiovascular walls with regard to changes of internal pressure, (d) possible further delay due to decreased pulsation on account of oblique projection of x-rays, (e) delay in transmission of ventricular pressure changes to the respective atrium. The last three are particularly important and may explain some of the tracings where the rise of the pulmonic pulse seemed to occur *after the end* of the first sound. Fig. 7-4 of these authors, on the other hand, shows that the rise of the pulmonic pulse coincides with the central phase of the first sound. It is apparent that the tricuspid valve must have closed earlier.

2. Exact measurements of intracardiac or intravascular pressure in normal persons are required for any definite conclusion.

3. As evidence of our statements, we present two superimposed tracings of pressure (right ventricular and pulmonic) with electrocardiograms and medium-frequency phonocardiograms in a normal child (Fig. 12). They reveal that closure of the tricuspid valve occurs in the very first part of the first sound (first arrow on ventricular pressure tracing); and that opening of the pulmonic valve occurs slightly later (second arrow), coinciding with a central vibration of the sound. In this tracing, there are three groups of vibrations (not four), probably on account of simultaneous mitral and tricuspid closure.

A.

B.

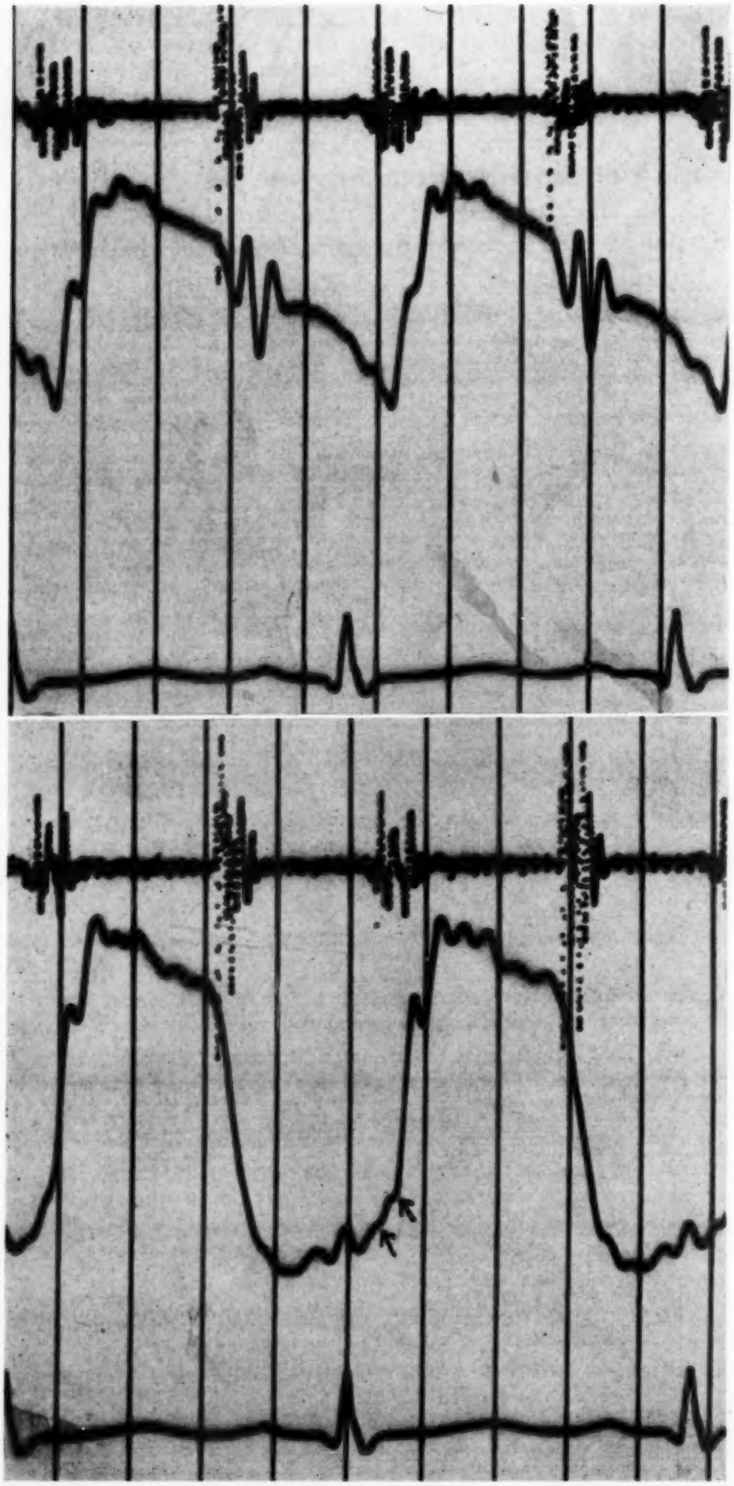

Fig. 12.—Superimposed tracings of a 6-year-old child whose heart presented normal findings. *A*, Phonocardiogram over third left intercostal space (filter 100-250); pressure in pulmonary artery. ECG. *B*, Phonocardiogram over same area and with same filtration; pressure in right ventricle; ECG.

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A Bedside Test for Peripheral Venomotor Reactions, With Demonstration of a Defect in Portal Cirrhosis

John J. Duggan, M.D., Howard Albright, M.D., and Thomas J. Murphy, M.D.
Syracuse, N. Y.

Although the venous side of the circulation is important in circulatory adjustments, study of venomotor reactions in man has been difficult. In one approach to this study, a segment of forearm vein was temporarily isolated from the circulation by externally applied clamps.[1,2] In such a segment of constant volume, changes in venous tone are reflected by changes in intraluminal pressure. Page and his associates[3] refined this technique and extended its application. Burch and Murtadha[4] used weights rather than clamps to produce external occlusion. Peripheral venoconstriction has been demonstrated in response to cold, hyperventilation, hypercapnia, apprehension, tilting, exercise, inspiration against resistance, and the Valsalva maneuver.

However, the occlusive technique has certain limitations. The presence of a needle in the vessel under study may induce a variable degree of venospasm. Venodilator responses are suspect because falls in pressure may be produced also by leakage from the isolated segment. Furthermore, external occlusion stops intraluminal blood flow and interferes with circulation in the vasa venarum so that the effects of circulating vasoactive substances cannot be easily studied.

It was demonstrated by Sir Thomas Lewis[5] that the pressure in a forearm vein distal to an occluding cuff comes within 1 minute to equal the pressure within the cuff over a range of pressures less than arterial. Lewis further pointed out that, so long as pressure within a vein is constant, changes in tone of the vessel will be reflected by changes in its diameter. It was found previously that encirclement of a peripheral vein with a local anesthetic agent led to the disappearance of neurogenic responses in the vessel distal to the block.[2] These principles have been combined in an effort to establish a bedside test for peripheral venomotor reactivity.

METHODS

The subject lay recumbent in bed at comfortable, but not controlled, ambient temperatures. Studies were discontinued during periods of excessively hot weather.

A forearm or hand vein was encircled midway in its course with 2 per cent Xylocaine. When no sufficiently long vein was available, two veins were chosen and a circle of Xylocaine placed

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From the Medical Service, Veterans Administration Hospital, Syracuse, N. Y., and the Department of Medicine, State University of New York Upstate Medical Center, Syracuse, N. Y.

Received for publication Sept. 20, 1957.

proximally around one. In either case, an innervated vein and a functionally denervated segment were available for study. The denervated segment served as a control for neurogenic reactions, and as an indicator for responses to circulating vasoactive substances. A blood pressure cuff around the arm was inflated to 15 mm. Hg. After 1 minute the external diameters of both segments were measured alternately with calipers, until three successive measurements of each were reproducible within a range of plus or minus 0.2 mm. The stimulus under study was then applied and measurements continued at 10-second intervals during its application and until vein diameter had returned to base-line levels.

The stimuli used most often were immersion of the opposite hand in ice water for 1 minute, voluntary hyperventilation for 1 minute, and breathing of a 5 per cent CO_2, 95 per cent O_2 mixture for 4 or 5 minutes. Other stimuli included bicycle exercise at a rate chosen by the subject as representing definite but not exhausting exertion, tilting on a table from the horizontal to 75°, immersion of the opposite hand in warm water for 1 minute, total body heating with an electric blanket, and inhalation of amyl nitrite.

All subjects were male. The normal group included 12 medical students and physicians who were 21 to 33 years of age, and 7 patients without demonstrable organic disease ranging in age from 32 to 62 years.

Four patients with diabetic neuropathy were studied. Their ages were 31, 39, 50, and 59 years. Each had severe disease with orthostatic hypotension, impotence, and plantar ulcers. None had evident neuropathy in the upper extremities where superficial and deep sensation, muscle strength, tendon reflexes, and sweating were clinically normal.

Thirteen male patients with frank liver disease, ranging in age from 25 to 72 years, were selected. Each had spider angioma and palmar erythema, many had red fingertips, and a few had clubbed fingers. Three were jaundiced at the time of study. None had evidence of peripheral neuropathy, and none was stuporous.

RESULTS

Normal Subjects.—Changes in diameter of forearm veins in normal subjects in response to selected stimuli are summarized in Table I and presented graphically in Fig. 1. The "blocked segment" is vein immediately distal to an encircling ring of a local anesthetic agent.

Ice water: In 25 trials in 18 normal subjects, the measured external diameter of the innervated vein regularly became smaller while the denervated segment showed little or no change. This stimulus was applied also at the end of each experiment in order to check for persistence of effective nerve block. These terminal responses fell within the same range but they are not reported here because proper care was not taken to establish return to base-line readings. In an effort to provide a quantitative expression of normal responses, results were calculated in terms of per cent of change in initial diameter. The mean change in diameter of the innervated vein was −41 per cent, with a standard deviation of 11 per cent, while there was no significant change in the denervated segment.

Hyperventilation: In these subjects, hyperventilation is essentially as effective a stimulus as ice water. However, because it requires the cooperation of the subject and cannot be standardized easily, its application to patients is limited. A direct vasodilator effect of hypocapnia[6] was not observed in the denervated venous segments of normal subjects nor in the superficial forearm veins of patients with postural hypotension due to diabetic neuropathy.

Exercise: A neurogenic venoconstrictor response was observed uniformly during the first minute of exercise. After 2 or 3 minutes, particularly with vigorous exercise, an irregular waxing and waning in size of the vein appeared.

TABLE I. CHANGES IN DIAMETER OF FOREARM VEINS IN RESPONSE TO VARIOUS STIMULI

STIMULUS	SUBJECTS	TRIALS	CHANGE IN DIAMETER OF VEIN						SIGNIFICANCE OF DIFFERENCE†
			INNERVATED SEGMENT			BLOCKED SEGMENT*			
			RANGE (MM.)	MEAN (MM.)	MEAN (% OF INITIAL DIAMETER)	RANGE (MM.)	MEAN (MM.)	MEAN (% OF INITIAL DIAMETER)	
Ice water (1 min.)	18	25	−1.2, −3.0	−2.0	−41.3	+0.3, −0.3	−0.1	−1.7	$p < 0.001$
Hyperventilation (1 min.)	12	12	−1.1, −2.6	−1.6	−36.1	0.0, −0.4	−0.1	−1.8	< 0.001
Exercise (1 min.)	7	7	−0.9, −1.7	−1.3	−26.9	+0.2, 0.0	0.0	−1.2	< 0.001
5 per cent CO_2 (5 min.)	10	10	+2.0, +0.4	+0.9	+17.5	+1.2, 0.0	+0.6	+13.0	N.S.
Tilt (1 min.)	4	4	−0.7, −3.3	−2.1	−25.8	+0.6, +1.5	+0.3	−1.2	0.05
Warm water (1 min.)	5	7	−0.4, 1.1	+0.7	+6.7	0.0, +1.1	+0.2	0.5	< 0.05

*Vein distal to an encircling ring of a local anesthetic agent.
†Mean change in per cent of initial diameter, innervated versus blocked vein.

Five per cent CO_2 inhalation: Hypercapnia produced dilatation of the superficial vein whether innervated or not. The reflex venoconstrictor response which was consistently demonstrable in the venous segment isolated from the circulation[2] was not apparent in the vein with an undisturbed circulation. Although there was no difference between the reactions of the innervated and denervated segments, the dilatation in each was significantly different from control values ($p < 0.001$).

Other stimuli: The venoconstrictor response to head-up tilting described by Page was apparent in this study. However, although the direction of change was clear, changes in the position of the forearm made measurement difficult. Immersion of the opposite hand in warm water produced dilatation of small magni-

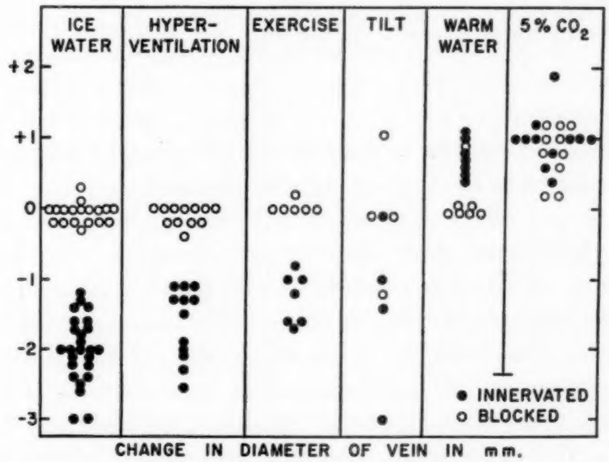

Fig. 1.—Response of forearm veins in normal subjects to simple stimuli. The "blocked" vein is vein distal to an encircling cuff of a local anesthetic agent. (Neg. 810 B, Medical Illustration Laboratory, Syracuse V. A. Hospital, Syracuse, N. Y.)

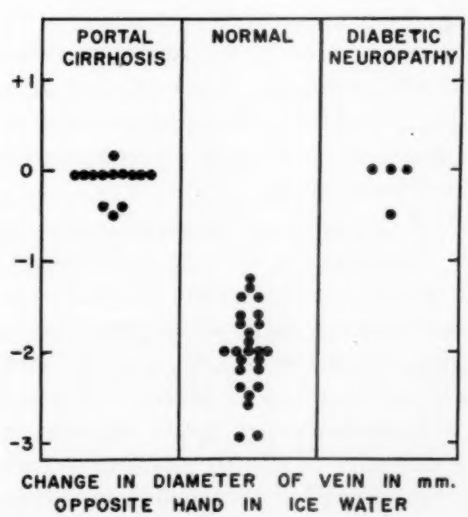

Fig. 2.—Reaction of forearm veins in response to immersion of the opposite hand in ice water for 1 minute. (Neg. 810 B, Medical Illustration Laboratory, Syracuse V. A. Hospital, Syracuse, N. Y.)

tude limited to the innervated vein. Total body heating produced dilatation of both segments but the reactions were slow in onset and in disappearance. Dilatation of both innervated and blocked segments was produced by the inhalation of amyl nitrite in 3 subjects.

Diabetic Neuropathy.—Each of the 4 patients with severe diabetic neuropathy failed to show significant response to ice water or to hyperventilation (Fig. 2). Similar lack of reaction was found by Page and his associates[3] in their patients with diabetic neuropathy studied by the occlusive clamp technique.

Portal Cirrhosis.—None of the patients with cirrhosis showed a normal response to ice water (Fig. 2). Nine of 13 showed no measurable venoconstriction, and the maximum change in vein diameter was −0.5 mm. (−8 per cent). Hyperventilation was similarly ineffective in these patients, even though it was carried to the point of symptoms in each of them.

DISCUSSION

This method for the study of peripheral venomotor reactions has proved to be convenient for bedside use and applicable to most patients. When the intact vein is studied, the procedure is painless and the vein untraumatized. When the local anesthetic is infiltrated about the vein, only transient discomfort is produced. Thus, artefacts due to psychic stimuli and to local trauma are minimized. In addition, intraluminal pressures are kept constant and within a physiologic range. This preparation is furthermore superior to the isolated segment in that venous response to a circulating stimulus has been demonstrable during hypercapnia and during total body heating. It is not suitable for the study of brief responses such as the venoconstriction due to a single inspiration, nor for procedures which may produce large elevations in systemic venous pressure such as the Valsalva maneuver. Measured changes in vein diameter are small, and the measurements are subjective.

With the exception of 5 per cent CO_2 breathing, the venomotor responses described here agree in direction with those previously defined for forearm vessels in man by use of the isolated segment. Lack of agreement in response to 5 per cent CO_2 breathing is due presumably to a dominant local effect of hypercapnia when the circulation of blood in the vein is not compromised, with extinction of the neurogenic constrictor response.

Although direction of change is of greatest interest in defining normal responses, a quantitative expression of change is necessary in order to separate normal from abnormal venomotor reactivity. Calculation of change in volume from measurement of one external diameter is precluded by the possibility that the relaxed vein is elliptical in cross section, and by lack of knowledge of the contribution of vein wall to external diameter. A quantitative expression of change in venous tone has not been attempted because of these considerations and because of lack of knowledge of certain physical characteristics of the vessels studied.[7] Recognizing that change in observed diameter is not a simple function of change in tone and that the veins measured were not identical in size and structure, the comparison of per cent of change in diameter remains useful. By this

means, using immersion of the contralateral hand in ice water as the stimulus, a statistically significant failure of response has been demonstrated in patients with diabetic neuropathy (in confirmation of the results of Page and his associates) and in patients with portal cirrhosis.

Easily standardized and suitable for bedside use, immersion of the opposite hand in ice water was consistently effective in normal subjects. Particularly in subjects who have experienced the stimulus previously, anticipation of ice water may produce peripheral venoconstrictions.[2,3] However, this anticipatory response had the temporal characteristics of a purely neurogenic one,[2] and no evidence for a circulating factor was seen in these experiments. Thus, a possible psychogenic component in the response to ice water does not detract from its utility as an index of neurogenic venomotor responses.

The failure of neurogenic venomotor response in the presence of advanced portal cirrhosis is not surprising. Vasodilatation has been demonstrated previously in the systemic arterial system[8] and in arteriovenous anastomoses in the hand[9] in patients with cirrhosis. Failure of venomotor responses may be inferred from the clinical observation of cirrhotics bleeding from esophageal varices. Here, visible veins may be inappropriately large and soft in the face of severe blood loss.

The direction of change in tone in superficial forearm veins may not always be representative of changes in general venomotor tone. For instance, superficial vessels are exceptional because of their role in temperature regulation. Although venoconstriction was found consistently during the early minutes of bicycle exercise, continuation of exercise produced a waxing and waning in the size of the peripheral vein. This response may well have been due to conflicting needs for the redistribution of blood for exercise, on the one hand, and for the dissipation of heat, on the other. However, it is suggested that the reactivity of these vessels, without regard to the direction of change, may be representative of general venomotor reactivity.

SUMMARY

A bedside technique for the study of acute changes in tone in unobstructed superficial forearm veins has been described. A direct venodilator effect of hypercapnia has been demonstrated. Failure of normal reflex venoconstriction in response to immersion of the opposite hand in ice water has been observed in patients with advanced portal cirrhosis.

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Wolff-Parkinson-White Syndrome Simulating Myocardial Infarction

I. Kariv, M.D., Tel Hashomer Government Hospital, Israel

The difficulty in the electrocardiographic diagnosis of myocardial infarction in the presence of the Wolff-Parkinson-White syndrome (WPW) has been emphasized by many investigators.[1-3] Normally the spread of electrical excitation through the myocardium proceeds from the endocardial to the epicardial surfaces, so that electrodes facing the ventricular cavity (endocardium) record an initial negative deflection Q, and those facing the epicardium record an initial positive deflection R.

In myocardial infarction an electrical window is created in the myocardium so that epicardial leads record the cavity potentials as an initial negative deflection Q. In the WPW syndrome, electrical excitation is said to spread from epicardium to endocardium,[4] so that the electrode facing the ventricular cavity records an initial positive deflection. An initial positive deflection will appear, therefore, in epicardial leads when an electrical window is produced by myocardial infarction. This absence of the expected Q wave of myocardial necrosis is one source of diagnostic error.

A more common error is the diagnosis of uncomplicated WPW as myocardial infarction.[1-3] In the WPW syndrome a deep, wide Q wave occurs normally, usually in Leads III and aV_F and less frequently in Leads I and aV_L, without clinical or anatomic evidence of myocardial infarction (Fig. 1). These Q waves, wide, deep, and slurred, simulating those of myocardial necrosis, are explained by the majority of investigators as due to aberrant spread of electrical stimulation.

Without entering into a discussion of various theories of the mechanism of WPW and the production of the characteristic ventricular complex, let it be recalled that the ventricular complex may be said to consist of 2 portions: the early delta wave, and the later remainder of QRS.[5]

Lepeschkin,[6] in a frontal plane analysis of the QRS complex in WPW, demonstrated that if the delta wave has a left axis deviation of more than minus 30°, it will appear as a negative wave (Q) in Leads II, III, and aV_F, and if deviated to the right more than plus 90°, as a negative wave (Q) in Leads I and aV_L. In

Received for publication Aug. 6, 1957.

leads perpendicular to the delta wave axis, the delta wave will be isoelectric, so that in such leads the P-R interval will have a deceptively prolonged appearance.

CASE REPORTS

CASE 1.—A 55-year-old man entered the hospital with the diagnosis of fresh posterior wall myocardial infarction based upon pre-admission ECG (Fig. 2,*A*). In this tracing there is a wide, deep, and slurred Q wave (0.08 sec.) in Leads II, III, aV_F, and V_7 with depression of the S-T segment in chest leads V_1 to V_5. This pattern fulfills certain ECG criteria of fresh posterolateral infarction. However, some unusual details should be noted. The QRS complex is wide (0.12 sec.). The R waves are very tall in chest leads V_1 through V_5 and are slurred at the base of the ascending limb.

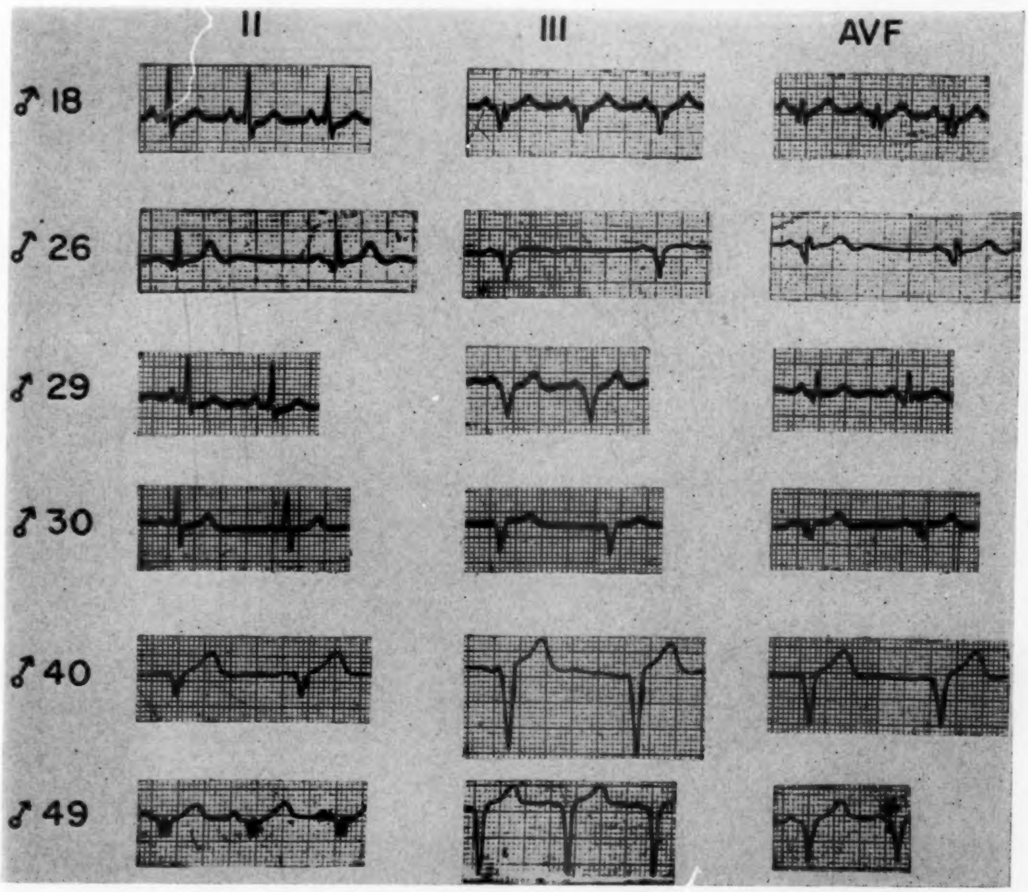

Fig. 1.—Leads II, III, and aV_F of 6 subjects with the WPW syndrome, all showing deep Q waves in Leads III and aV_F.

Clinically the patient appeared to be in excellent health. He gave no history of chest pain. The usual clinical manifestations of myocardial infarction were absent. Another ECG (Fig. 2,*B*), taken a few hours after admission and about 36 hours after the first, demonstrates that the S-T segments are now more nearly isoelectric, but that the wide Q waves persist in Leads II, III, aV_F, and V_6. On the basis of this tracing it was thought that the patient had an old posterior wall myocardial infarction and that the changes in S-T segment were probably due to digitalis and quinidine which had been prescribed for a long period prior to hospitalization.[7] In this tracing,

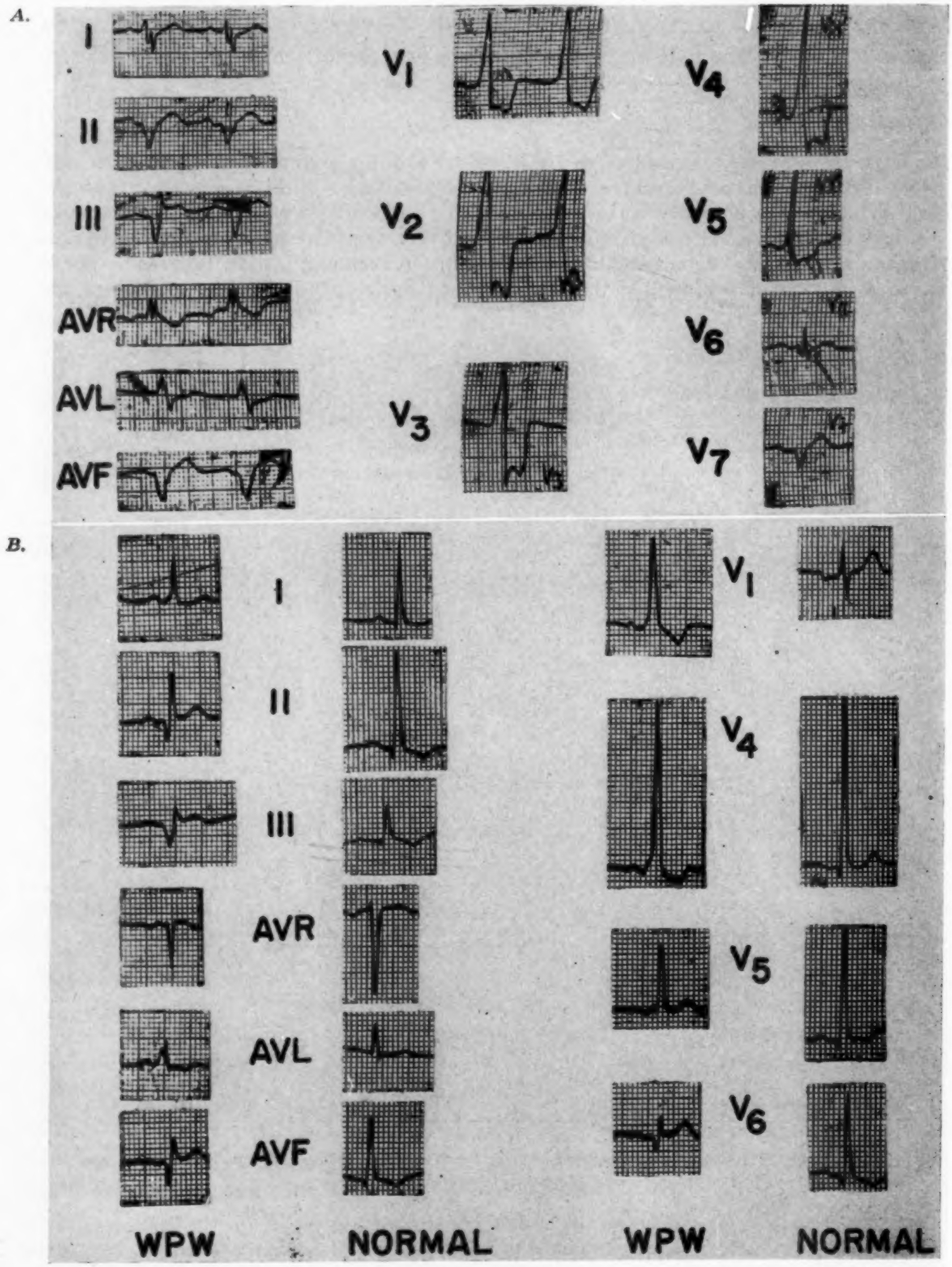

Fig. 2.—Case 1. *A*, ECG taken before admission to hospital, showing "typical" pattern of recent posterior wall myocardial infarction. *B*, The records labeled *WPW* were taken 36 hours after those shown in *A*. The pattern of WPW is now quite obvious. Note the deep and wide Q waves in Leads III and aV_F. The record labeled *Normal*, taken a few months later, shows the disappearance of the "pathologic" Q waves in Leads III and aV_F. When episodes of WPW recurred, the Q waves reappeared.

tall R waves with slurring of the upstroke in chest leads V_1 through V_5 were again noted and the possibility of WPW syndrome was considered in spite of normal or even prolonged P-R interval. This possibility was strengthened when direct questioning revealed a history of recurrent bouts of paroxysmal tachycardia, extending over a period of 20 years. A series of electrocardiograms taken over this long period was analyzed: all of them show the typical QRS complex and had been interpreted by different examiners on various occasions as indicating either interventricular conduction defect, or RBBB, or right ventricular hypertrophy. The diagnosis of WPW had never

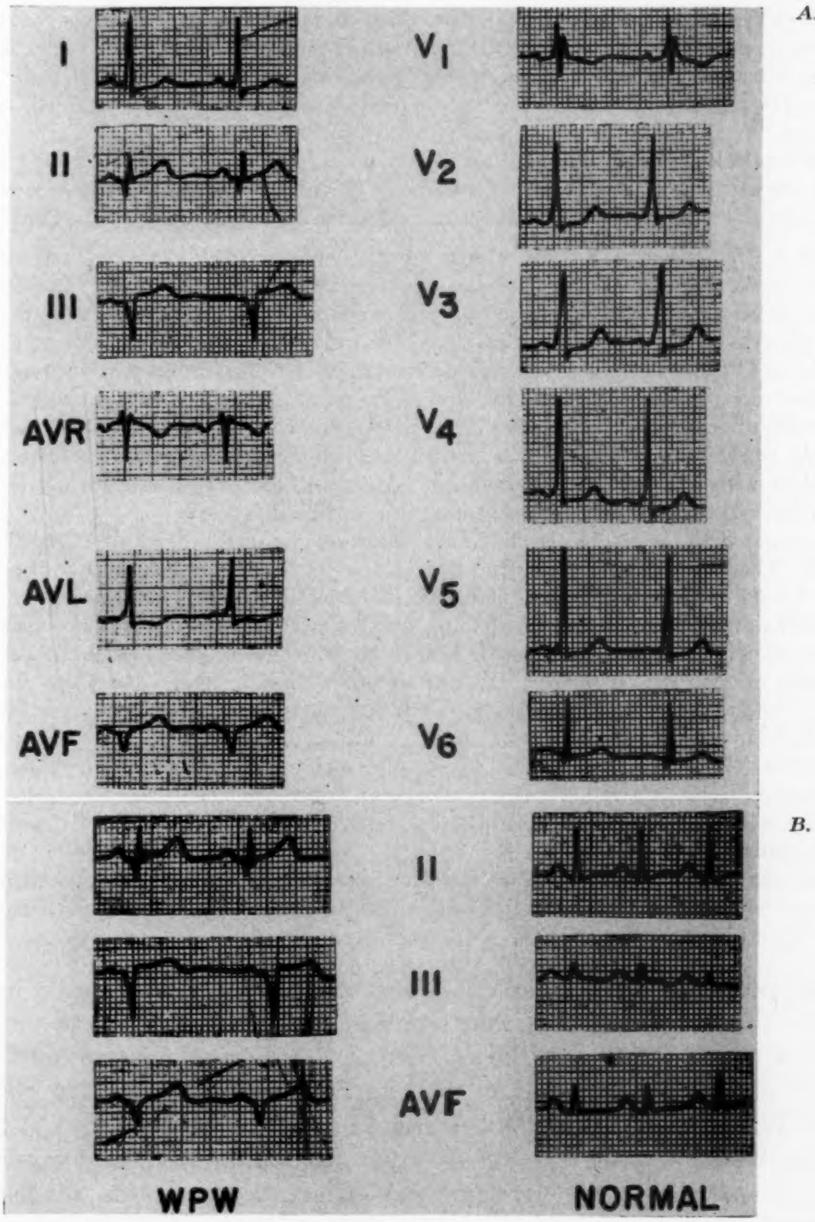

Fig. 3.—Case 2. *A*, ECG showing WPW pattern; deep Q waves in Leads III and aV_F, and incomplete RBBB. *B*, Leads II, III, and aV_F showing WPW syndrome and normal conduction. Note the disappearance of the "abnormal" Q waves.

been considered. In the tracing labeled WPW in Fig. 2,*B* the P-R interval equals 0.11 to 0.12 second in aV_L, 0.16 in Lead II. A definite delta wave is seen in Lead I and especially in aV_L and chest leads; delta waves are not seen in Lead II.

The QRS complex is wide (0.12 sec.) in those leads in which the delta wave is present, and appears normal (0.08 sec.) in Lead II in which the delta wave is not apparent. There is also a deep, wide Q wave in Leads II, III, aV_F, and V_6. At this point a diagnosis of old posterior infarction superimposed on WPW was made.

The patient returned for a follow-up examination several months later. In the interval he had felt well except for attacks of palpitation which occasionally lasted as long as a day. An ECG performed on this occasion revealed—for the first time during the period of observation—entirely normal conduction (Fig. 2,*B*). Most striking is the disappearance of the pathologic Q waves in Leads II, III, aV_F, and the left chest leads. When aberrant conduction returned, the Q waves reappeared.

The conclusions are obvious: (1) This patient suffers from WPW syndrome which is the cause of the attacks of paroxysmal tachycardia. (2) The Q waves do not indicate myocardial infarction but are the result of the aberrant conduction known as the WPW syndrome.

CASE 2.—A 32-year-old woman was seen because of an attack of paroxysmal tachycardia of a few minutes' duration which had occurred several days previously. Except for a bout of tachycardia of 20 minutes during pregnancy 6 years previously, she had always been in good health.

On physical examination the typical signs of mitral stenosis were found. The ECG (Fig. 3,*A*) shows changes "typical" of posterior wall myocardial infarction, with deep, wide Q waves in Leads II, III, and aV_F. Lead V_1, in addition, reveals incomplete right bundle branch block.

In view of the patient's age the diagnosis of myocardial infarction did not seem plausible One of the possibilities considered was that she had suffered at one time from subacute bacterial endocarditis with coronary artery embolism. However, the patient denied any fever or other serious illness in the past and had never received antibiotic therapy.

The patient was seen at intervals in the follow-up clinic and many electrocardiograms were recorded. The findings were constant in all tracings. Only after a diagnosis had been established in Case 1, and a high degree of suspicion aroused, was the abnormal configuration of the QRS complexes in the chest leads appreciated and WPW syndrome suspected. Although the M shape characteristic of incomplete right bundle branch block is present in V_1, there can be no doubt as to the delta wave in V_2, V_3, and V_4. On careful examination this anomalous form can be detected in Leads I and aV_L as well. It should be noted that, as in Case 1, the P-R interval in most leads is normal in duration (0.16 sec.).

Exercise following the injection of ½ mg. of atropine produced a marked change in the QRS configuration. This change was so transient that only limb leads were recorded (Fig. 3,*B*). Obviously, normal conduction is now present and the wide, deep "coronary" Q waves have disappeared from Leads II, III, and aV_F.

This return to a normal pattern leaves no room for doubt that this patient demonstrates aberrant conduction of the WPW type, and at the same time definitely dispels suspicion of myocardial infarction.

As previously noted, the appearance of a deep, wide Q wave in WPW is dependent upon the vector of the delta wave.

In 60 per cent of cases the vector has a left axis deviation, and only in 10 per cent of cases is it shifted to the right.[6] It is for this reason that in most cases of WPW the abnormal Q wave appears in Leads II, III, and aV_F, and that the mistaken diagnosis of anterior myocardial infarction (wide Q in Leads I and aV_L) is rare. In the following case, which demonstrates this less common variant of WPW, a diagnostic error of a different kind was made.

CASE 3.—An 18-year-old male, who had been beset by family difficulties, began to complain of bouts of precordial oppression, shortness of breath, and palpitation. He was admitted to another hospital, where he was found to have tachycardia which subsided spontaneously after a short

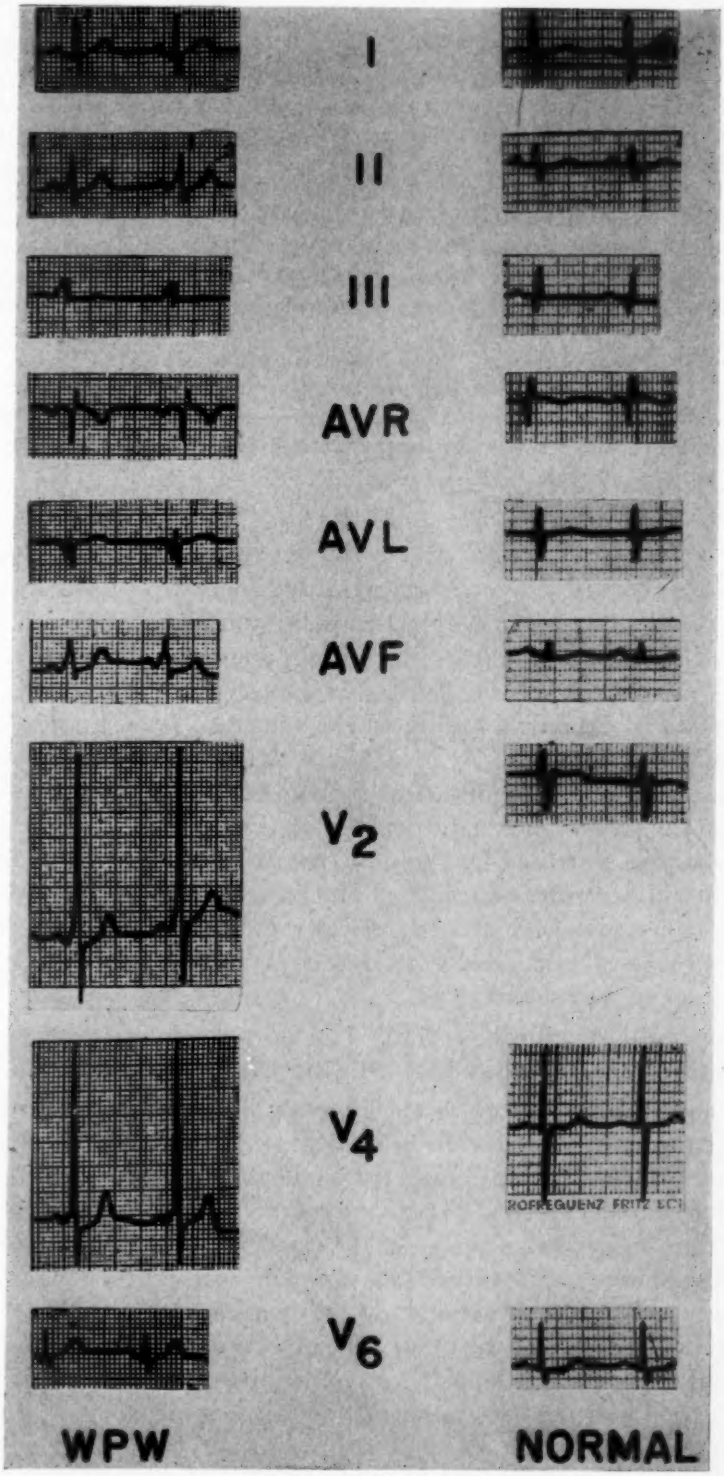

Fig. 4.—Case 3. ECG of WPW syndrome and of normal conduction. Note the disappearance of "pathologic" Q waves in aV_L in the normal ECG.

interval. These symptoms recurred several times. A systolic murmur was heard at times. On two occasions it was felt that fluoroscopy revealed some cardiac enlargement. Several electrocardiograms recorded during this hospitalization were all normal. He was discharged from the hospital with the diagnosis of paroxysmal tachycardia. The following possible etiological factors, each designated by a question mark, were listed: "Psychosomatic disorders?", "Thyrotoxicosis?", "Post-diphtheric myocarditis?", "Avitaminosis?".

When this patient was first seen by us, physical examination and fluoroscopy revealed no cardiac pathology. The electrocardiogram was distinguished by an abrupt change in the character of the QRS complex after the first beat recorded in aV_F; the QRS complex of the earlier leads and the first complex in aV_F is typical of the aberrant conduction in the WPW syndrome, while the later complexes show the normal pathway. Paradoxically, after exercise all complexes were of the WPW type (Fig. 4).

In this case the vector of the delta wave is deviated to the right so that wide, deep Q waves appear in Leads I and aV_L. In an older patient such Q waves may well have been interpreted as resulting from anterior myocardial infarction, and a serious diagnostic error would have been made.

The electrocardiograms recorded during the first hospitalization were reviewed and found to be, as stated, entirely normal.

DISCUSSION

The 3 cases of WPW syndrome presented in this report demonstrated abnormal Q waves: the first 2 cases in Leads III and aV_F; the last, in Leads I and aV_L. It is of interest to note that the correct diagnosis in Case 1 was not made at once in spite of the classic history of paroxysmal tachycardia and rather typical electrocardiographic findings, whereas in Case 2 the pattern was confused as right bundle branch block. It is apparent that a higher degree of suspicion is necessary since the WPW syndrome is far from being a rare entity. Such awareness will save the physician a great deal of concern and indecision in the interpretation of a tracing which at first glance may appear very complicated. More important, it will permit reassurance of the patient as to the nature and progress of his disturbance rather than iatrogenically increasing anxiety and heart-consciousness through a mistaken diagnosis of bundle branch block, ventricular hypertrophy, or myocardial disease.

Even after the diagnosis of WPW had been made in the first 2 cases, the possibility of myocardial infarction could not be entirely discarded.

Grant and Murray,[8] after vector analysis of electrocardiograms in patients with myocardial infarction and in normal controls, define what they call the Q area. This represents the initial negativity of the QRS complex during the first 0.04 second of depolarization. They arrived at the conclusion that the empiric conception that a Q wave as broad as, or broader than, 0.04 second is pathologic and indicative of myocardial infarction, and will be correct in 95 per cent of cases. Q waves narrower than 0.04 second are still within normal limits. In addition, the increase in the width of the Q wave in myocardial infarction occurs after the normal initial negativity of depolarization, i.e., after the first 0.02 second at least, and at the expense of the remainder of the QRS complex.

In WPW the QRS complex is in reality a fusion beat,[5] the first component being the delta wave and the second the normal remaining ventricular complex. The delta wave appears early and at the expense of the P-R interval because of premature excitation. It is the same delta wave which, as previously noted, is

responsible for the Q wave in WPW. In other words, the wide Q wave in WPW is the result of depolarization appearing *before* the normal Q rather than *after* the normal Q as in myocardial infarction.

If these considerations are correct, then the interpretations of the significance of the Q wave, whether representing only WPW or myocardial infarction, becomes in most cases a simple arithmetical procedure. The width of delta wave is subtracted from the width of Q; if the remaining late negativity is greater than 0.04 second, it must indicate the presence of infarction in addition to WPW; if less than 0.04 second, it is nothing but the result of the aberrant conduction. For example, in Case 1, Q_3 equals 0.08 second and delta equals 0.05 second; the remaining late negativity is 0.03 second—within normal limits—and therefore the possibility of infarction can be discarded (Fig. 5).

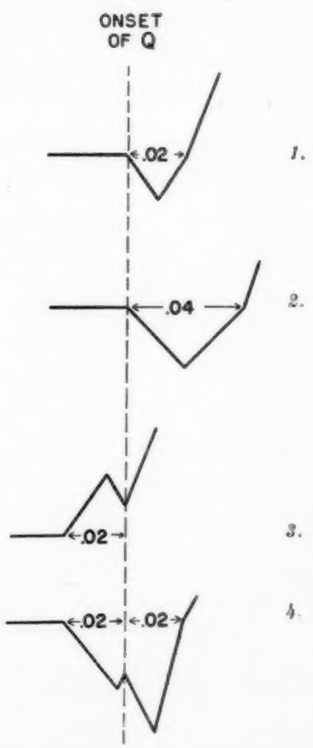

Fig. 5.—*1*, Normal Q wave, 0.02 sec. *2*, Wide pathologic Q wave of myocardial necrosis. *3*, Delta wave in the WPW syndrome appearing before the beginning of QRS and thus shortening the P-R interval. *4*, Inverted delta wave and normal Q wave giving the impression of pathologic Q wave.

In the 3 cases presented, additional proof of the absence of myocardial infarction was established by the disappearance of the pathologic Q waves when the aberrant pathway was replaced by normal conduction. This additional proof should be obtained in all doubtful cases, since normal conduction normally appears in WPW after exercise, atropine, quinidine, or combinations of these. We feel, however, that the theoretical considerations presented above are of interest in

that they permit the correct diagnosis of the WPW syndrome, and thereby allow us to decide whether there is associated myocardial infarction, as well as providing for a better understanding of the electrophysiology of the heart.

SUMMARY

Three cases of electrocardiographic pseudomyocardial infarction in the WPW syndrome are presented.

The deep, wide "infarct like" Q waves disappeared in all cases when aberrant conduction was displaced by the normal pathway.

The absence or presence of myocardial infarction associated with WPW can be determined simply by subtracting the width of delta wave from the width of the Q wave. If the remainder is 0.04 second or more, there is associated myocardial infarction; if less, aberrant conduction alone is responsible for the "pathologic" Q wave.

I wish to thank Prof. Dr. H. Heller, Chief of Medical Services, Government Hospital, Tel-Hashomer, for permission to study Case 1, and for his helpful criticism.

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Electrocardiographic Changes in the Dog During Hypothermia

Everton M. Santos, M.D., and C. Frederick Kittle, M.D., Kansas City, Kans.*

Various electrocardiographic changes during hypothermia in human beings and in numerous experimental animals have been described.[1,2,5,6,8,9,11,15,16] In general these have consisted of a progressive bradycardia with prolongation of P-R, QRS and Q-T intervals as the temperature decreases. The S-T segment and the T wave have been noted to vary by changes in their amplitude or by reversal in direction. Occasionally, normal sinus rhythm has been depressed and replaced by some of the lower situated pacemakers. There appears to be a fairly definite combination of these changes for each species.

During the course of recent experiments on the prevention of ventricular fibrillation in hypothermic dogs, electrocardiograms were taken. The present studies are concerned with their description and analysis.

METHODS

Electrocardiograms of 24 dogs were used in this analysis. Each dog was anesthetized with intravenous Nembutal (35 mg. per kilogram) and an endotracheal tube was inserted. The tube was then connected to an automatic ventilator supplied with oxygen. Throughout the entire experiment the animals were moderately hyperventilated. Cooling was done by immersion in ice water until a rectal temperature of 26 to 27 degrees centigrade was reached. The animal was then placed on the operating table and a right thoracotomy was done. Various drugs were subsequently utilized to investigate the incidence and prevention of ventricular fibrillation with right ventriculotomy. The lowest rectal temperature was usually between 22 and 25 degrees centigrade. After the thoracotomy the animal was rewarmed by immersion in warm water (42° to 45° C.).

Electrocardiograms (Lead II) were obtained intermittently throughout the experiment. The electrocardiographic findings discussed here are those related to hypothermia alone and are not pertinent to the drugs administered.

DISCUSSION

Table I shows the average rate, the P-R, the QRS, and the Q-T-intervals in these animals before thoracotomy at normal body temperature, at 30°C., and at 28°C., and after thoracotomy at the lowest temperature of the animal (22° to 25°C.).

From the University of Kansas Medical Center, Kansas City, Kans.
Supported by U. S. P. H. S. Grant H-1331, Department of Surgery, University of Kansas Medical Center, Kansas City, Kans.
Received for publication Sept. 23, 1957.
*Presently, Fellow in Thoracic Surgery at Emory University Hospitals, Emory University, Ga.

Progressive slowing of the heart rate was noted with decreasing temperatures. There was a fairly constant decline in the temperature ranges discussed here (Fig. 1).

TABLE I. CARDIAC RATE, P-R, QRS, AND Q-T INTERVALS BEFORE AND AFTER THORACOTOMY IN HYPOTHERMIA (AVERAGE OF 24 DOGS)

	BEFORE THORACOTOMY				AFTER THORACOTOMY
	NORMAL	30°	28°	27°	22°—25°
Rate	147	87	65	55	47
P-R	0.10	0.13	0.15	0.16	0.17
QRS	0.05	0.07	0.08	0.08	0.09
Q-T	0.23	0.40	0.57	0.66	0.71

Sinus rhythm was the basic rhythm in all animals and remained so to their lowest temperature unless ventricular fibrillation supervened. Specifically, in the temperature range studied there was no depression in site of impulse formation nor did other arrhythmias occur. This is in marked contrast to the arrhythmias noted in a recent report on 25 human beings operated upon for congenital heart disease,[7] but is consistent with the electrocardiographic findings in normal monkeys during hypothermia.[1]

One change consistently found was that of notching, slurring, and increased width of the P waves resulting in an "M" pattern, the second leg of the "M" being usually the taller and more prolonged. This reflects a slowing of conduction and increased time of depolarization more pronounced in the left atrium (Fig. 2).

Progressive lengthening of the P-R and QRS intervals was found with decreasing temperature and decreasing heart rate. Both correlate well with slowing of the heart rate and are probably related to the decreased metabolic demands or the delayed conduction within the heart during hypothermia (Fig. 3).

Considerable prolongation of the Q-T interval was noted, not correlated with the progressive bradycardia as shown by the index of Bazett (Table II).

Since the Q-T interval is a measure of depolarization and repolarization within the ventricular muscle, the prolongation of this interval probably represents an alteration in metabolism of the ventricular muscle during hypothermia.[10] We believe this prolongation of the Q-T interval to be an important observation during hypothermia, possibly reflecting minute changes in calcium or potassium equilibrium within the myocardium, not shown by serum chemical analysis.[4]

TABLE II. CONSTANT (K) OF BAZETT FOR Q-T INTERVAL DURING HYPOTHERMIA (AVERAGE OF 24 DOGS)

	BEFORE THORACOTOMY				AFTER THORACOTOMY
	NORMAL	30°	28°	26°	22°—25°
K	0.83	1.07	1.21	1.32	1.47

Fig. 1.—This illustrates a typical sequence of electrocardiographic changes in a dog cooled from 37.5° to 23.75° C. Sinus rhythm is present at all temperatures although it decreases from an initial 214 to 40 per minute at 23.75°C. The P-R interval increases from 0.10 to 0.20 second, the QRS from 0.04 to 0.09 second, and the Q-T from 0.20 to 0.86 second. Note the bizarre elevation of the S-T segment at 23.75°.

Marked deviations and abnormal patterns were seen in the S-T segment and the T waves (Figs. 1, 3, and 4). This has been noted previously in experimental animals[5,6] and also in two of the reported cases of accidental hypothermia.[11,15] Usually an elevation of the S-T segment occurred immediately following the QRS complex. In some instances the confluence of this elevation with the QRS complex made it difficult to delineate the end of depolarization. This alteration has been termed "injury potential" when seen at normal temperatures and has been

A.

B.

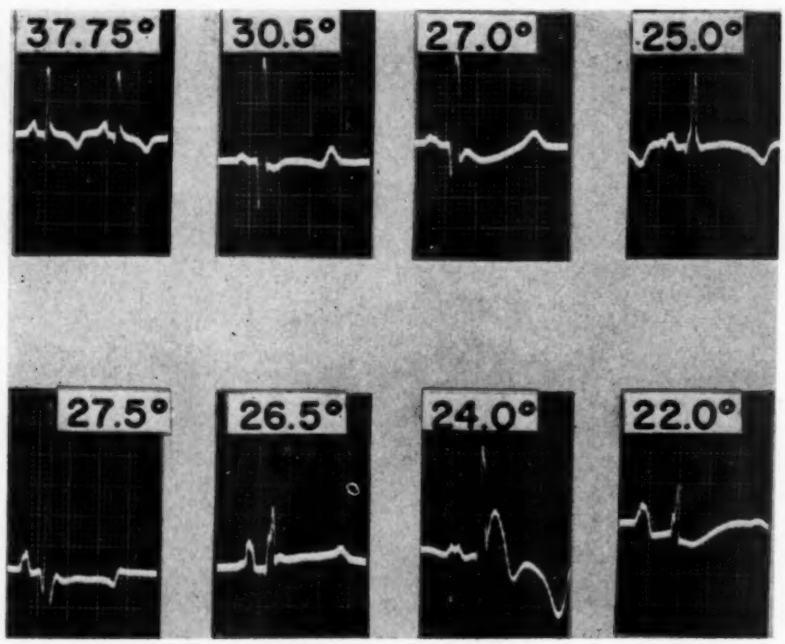

Fig. 2.—*A*, Shows the broadening and notching of the P wave as the temperature drops from 37.75° to 25°C. *B*, Shows different examples of P wave changes at temperatures varying from 27.5° to 22° C.

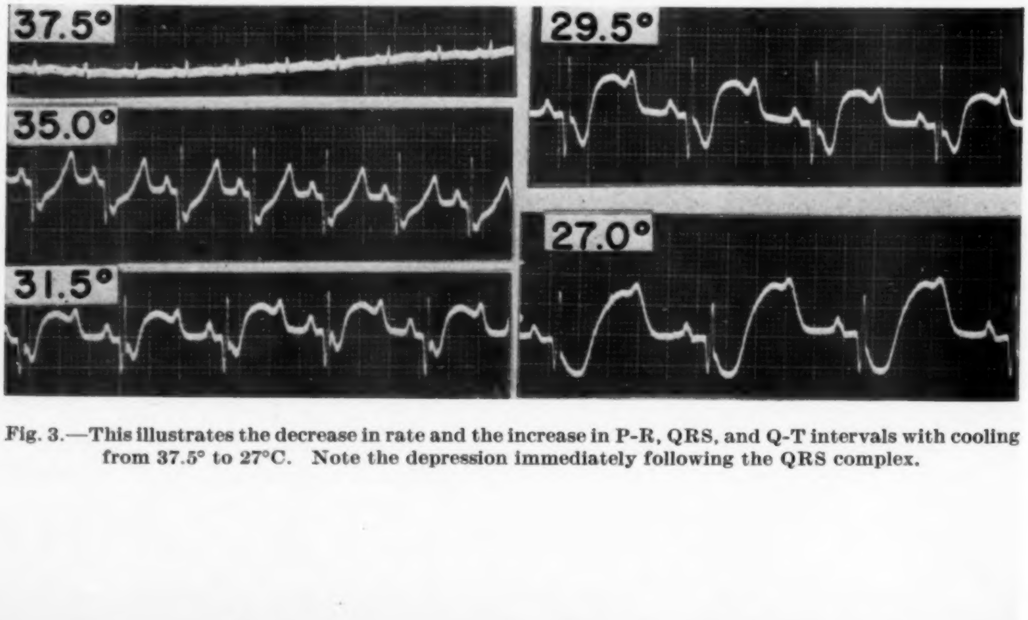

Fig. 3.—This illustrates the decrease in rate and the increase in P-R, QRS, and Q-T intervals with cooling from 37.5° to 27°C. Note the depression immediately following the QRS complex.

attributed by some to a respiratory acidosis.[3] In our experiments it did not appear due to acidosis since all animals were made alkalotic by hyperventilation with oxygen, their average pH being 7.68. Morphologically there is a striking difference between the configuration of this segment as seen in hypothermia and the classically described "current of injury" pattern associated with the acute phase of myocardial ischemia (Fig. 5).

In a few of the animals a depression of the S-T segment was noted instead of the previously mentioned elevation. In some instances the depression persisted without the appearance of elevation, but in others it was replaced by an elevation as lower temperatures were reached.

No constant relation between the presence or absence of either elevation or depression of the S-T segment and the occurrence of ventricular fibrillation could be found, and no prognostic significance could be ascribed to these changes. Furthermore, we could not detect any abnormal electrocardiographic features in hypothermia to be of value in indicating the subsequent occurrence of ventricular fibrillation.

The described electrocardiographic changes were reversible with rewarming and restoration to normal temperature. This lends support to the concept that

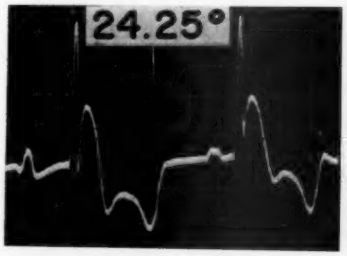

Fig. 4.—Another example of S-T segment elevation, 24.25°C.

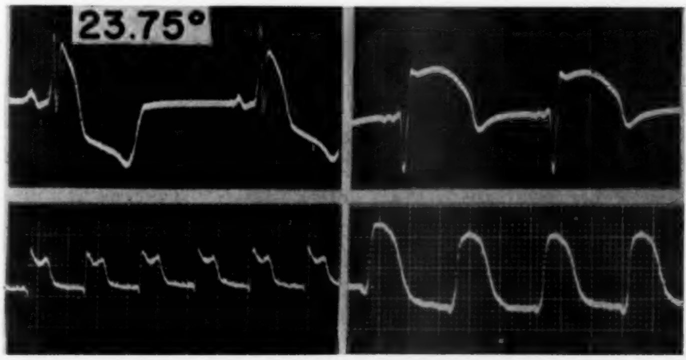

Fig. 5.—Comparison is made between the S-T segment changes occurring in hypothermia (left upper strip) and in three instances of acute myocardial ischemia following defibrillation during hypothermia (right upper strip), ligation of the anterior coronary artery in a normothermic dog (left lower strip), and acute myocardial infarction in man (right lower strip). The difference in the pattern of the S-T segment is obvious.

deviations from normal in hypothermia are chiefly functional and that no permanent anatomic results occur during hypothermia of the duration and degree studied here.

SUMMARY

1. Electrocardiographic observations during hypothermia are analyzed. The rate decreased proportionately to the temperature, as did prolongation of the P-R and the QRS intervals.

2. Prolongation of the Q-T intervals was greater than expected by decrease in cardiac rate alone. Its lengthening during hypothermia reflects altered metabolism of the ventricular muscle. This may be due possibly to minute changes in calcium and potassium not detectable by present serum analyses.

3. Various morphologic changes in P wave and the S-T segment are discussed.

4. No prognostic significance as to the occurrence of ventricular fibrillation could be derived from the electrocardiogram during hypothermia.

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Loculated Pleural Effusion in Congestive Heart Failure Due to Severe Anemia: Report of a Case

L. M. Sanghvi, M.R.C.P. (London), D.T.M. & H. (England), and S. N. Misra, M.B.B.S., Jaipur, India

Higgins and associates[1] in a review of the literature collected 41 authenticated cases of loculated pleural effusion due to congestive heart failure, and 4 other cases have been added since.[2] There is only a single instance of a paramediastinal effusion[3] and none with anemia as the etiological factor of congestive failure.

CASE REPORT

N., a 25-year-old woman, was admitted on March 5, 1957, for severe anemia due to chronic malaria of 3 years' duration. On examination the patient had severe congestive failure with orthopnea, engorged neck veins, generalized anasarca and ascites, and liver enlarged 4 inches below the costal margin. The spleen was palpable 3 inches below the costal margin and there were signs of fluid in the right chest anteriorly. The heart was considerably enlarged with systolic mitral and pulmonary murmurs and a pulmonary systolic thrill.

Laboratory examination revealed a red cell count of 1.25 millions per cubic millimeter, hemoglobin 2 Gm. per cent, arm-to-tongue circulation time 12 seconds, venous pressure 29 cm. of normal saline, and a negative Kahn test. An electrocardiogram showed nonspecific S-T changes and left ventricular hypertrophy pattern. A posteroanterior roentgenogram of the chest (Fig. 1,*A*) showed considerable enlargement of the cardiac shadow on the left and a density on the right side simulating enlarged right heart but with hazy margins. A lateral view (Fig. 1,*B*) disclosed that the density was superimposed on the cardiac shadow in the anterior inferior mediastinum with its upper end tapering anteriorly to the manubriosternal junction.

On paracentesis in the fourth right intercostal space anteriorly, 150 c.c. of clear amber colored fluid could be drawn out, the fluid being a transudate with 2.9 Gm. per cent of protein and 5 cells per cubic millimeter. A pericardial tap revealed absence of any fluid.

With treatment directed at correction of the anemia, the patient made a rapid and uneventful recovery. An artificial pneumothorax could be successfully induced 3 months later when the anemia was cured, and a roentgenogram (Fig. 1,*C*) clearly demonstrated absence of pleural symphysis although the heart was still slightly enlarged.

COMMENT

In the case reported above, presence of a loculated pleural effusion was suspected clinically. The density in the posteroanterior roentgenogram closely

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From the Department of Cardiology, Sawai Man Singh Hospital and Medical College, Jaipur, India.
Received for publication Aug. 26, 1957.

simulated enlarged heart on the right side, but the diagnosis was confirmed by a lateral view and a pleural tapping. The effusion was paramediastinal and in the anterior inferior mediastinum, while in the case reported by Di Maio[3] it was in the anterior superior mediastinum. That obliteration of the general pleural

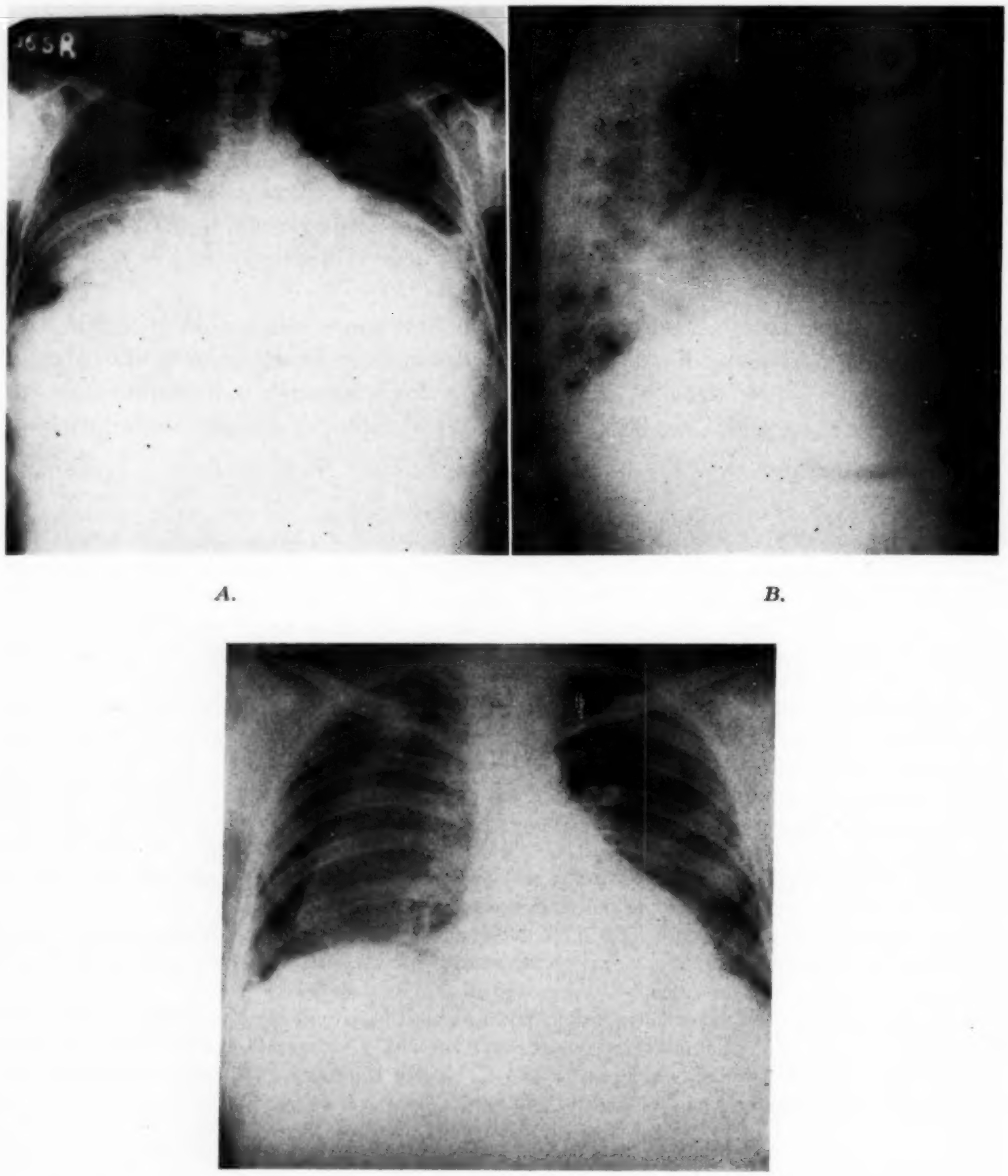

Fig. 1.—*A*, Posteroanterior roentgenogram of the chest on March 6, 1957, showing considerable cardiac enlargement on the left, and a paramediastinal density on the right side closely simulating cardiac enlargement. *B*, Lateral view showing that the density is superimposed on the cardiac shadow in the anterior inferior mediastinum. Its upper end tapers anteriorly to the manubriosternal junction and clearly shows that it is not due to cardiac shadow. *C*, June 21, 1957. Successful artificial pneumothorax demonstrating absence of obliteration of the general pleural cavity.

cavity by adhesions is not necessarily a prerequisite for the occurrence of a loculated effusion in congestive heart failure had been noted in two instances previously where an effusion occurred in the general pleural cavity after the disappearance of the loculated effusion.[2,4] In the present case this has been clearly demonstrated by a successful artificial pneumothorax 3 months after the disappearance of the loculated effusion.

SUMMARY

A case of severe anemia is reported with a loculated paramediastinal effusion due to congestive heart failure. Absence of pleural symphysis was demonstrated by a successful artificial pneumothorax 3 months after the disappearance of the loculated effusion.

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Effects of Tolazoline Hydrochloride (Priscoline†) on Circulatory Dynamics of Patients With Pulmonary Hypertension

Abraham M. Rudolph, M.D., Milton H. Paul, M.D.,** Leonard S. Sommer, M.D., and Alexander S. Nadas, M. D., Boston, Mass.*

Pulmonary arterial hypertension may be due to an increased pulmonary blood flow, to an increased resistance to flow in the small pulmonary vessels, or to a combination of both factors. Pulmonary hypertension on the basis of increased blood flow is frequently encountered in patients with congenital heart disease with a communication between the systemic and pulmonary circulations (patent ductus arteriosus, ventricular septal defect). Surgical closure of the communication results in a reduction of pulmonary pressure. Pulmonary arterial hypertension due to increased vascular resistance is encountered in chronic pulmonary disease, kyphoscoliotic heart disease, mitral valve disease, congenital heart disease, chronic pulmonary embolic disease, and primary pulmonary hypertension. The possible mechanisms by which these conditions result in increased pulmonary vascular resistance have not been established. Organic vascular changes in the small pulmonary vessels are usually demonstrable and appear to constitute the major obstructive factor. Occasionally, the clinical syndrome of pulmonary vascular obstruction has been encountered and no pulmonary vascular changes observed at autopsy.[1] Therefore, the possible role of pulmonary vascular spasm as an isolated or associated factor should be considered. The pulmonary vasculature has been regarded usually as being particularly unresponsive to most drugs,[2,3] and no powerful vasodilator effect has yet been demonstrated. Dresdale and associates[1,4] reported the efficacy of tolazoline hydrochloride in reducing pulmonary vascular resistance in several patients with primary pulmonary hypertension.

The present study concerns the effects of acute intravenous administration of tolazoline on the pulmonary and systemic arterial pressures, the pulmonary and systemic blood flow, and the pulmonary and systemic vascular resistance in patients with pulmonary arterial hypertension associated with congenital heart disease.

From the Department of Pediatrics, Harvard Medical School, and the Sharon Cardiovascular Unit, Children's Medical Center, Boston, Mass.
Supported by a Grant-in-Aid from the American Heart Association.
Received for publication Sept. 6, 1957.
*Research Fellow, American Heart Association.
**Special Research Fellow, United States Public Health Service.
†Registered trademark.

MATERIAL AND METHODS

Observations of the effect of acute intravenous administration of tolazoline were made in 10 patients, aged 3½ to 29 years, during the course of cardiac catheterization. All 10 patients had severe pulmonary arterial hypertension with markedly increased pulmonary vascular resistance; 5 had associated ventricular septal defects; 2 had patent ductus arteriosus; 2 had atrial septal defects; and 1 had no demonstrable cardiac anomaly.

Since it was felt that drugs used for premedication may modify the responses to tolazoline, two types of premedication were used. Morphine and Nembutal were given to 5 patients, and a Demerol, Phenergan, chlorpromazine combination to the other 5 patients. Cardiac catheterization was performed by the usual techniques. Pressures were recorded with Sanborn capacitance manometers on a four-channel direct-writing oscillograph. Blood oxygen content was measured by the manometric method of Van Slyke and Neill. Oxygen consumption was measured by collection of expired gas samples before and after tolazoline administration. In the 3 youngest patients these samples could not be obtained, and oxygen consumption of 180 ml./min./M.^{2} was assumed. Since oxygen consumption did not change after tolazoline administration in the 7 patients in whom it was measured, it was assumed it did not change in the other 3.

Pulmonary wedge blood samples and pressures were obtained in 5 patients before and after tolazoline administration. The blood samples all showed 98 to 100 per cent oxygen saturation and, in those patients in whom it was not obtainable, oxygen saturation of pulmonary venous blood was assumed to be 98 per cent. Pulmonary wedge pressures did not change by more than 2 mm. Hg after tolazoline administration, and for this reason it was assumed that pulmonary venous pressure did not alter significantly after tolazoline administration in any of the patients. When pulmonary wedge pressures were not obtained, pulmonary venous mean pressure was assumed at 3 mm. Hg above right atrial mean pressure.

Pulmonary and systemic blood flows were calculated by the Fick principle. Since the catheter tip was left in the main pulmonary artery, it was not possible to measure simultaneous pulmonary and systemic flows in the presence of a left-to-right shunt. In order to determine systemic and pulmonary flow simultaneously in 3 patients a second catheter was inserted through a separate vein at the site of insertion of the first catheter, and it was advanced to the right atrium to obtain mixed venous blood.

Pulmonary and systemic vascular resistances were expressed as mm. Hg/L./min./M.^{2} and were determined from the usual formulae:

$$R_p = \frac{\text{PA m} - \text{PV m}}{Q_p} \qquad R_s = \frac{\text{SA m} - \text{RA m}}{Q_s}$$

R_p, R_s = pulmonary, systemic resistance
PA m = mean pulmonary arterial pressure
PV m = mean pulmonary venous (wedge) pressure
SA m = mean systemic arterial pressure
RA m = mean right atrial pressure
Q_p, Q_s = pulmonary, systemic blood flow, L./min./M.^{2}

After the routine diagnostic catheterization procedure was completed, control pulmonary arterial and brachial arterial pressure and blood samples were obtained during a 3-minute period of collection of an expired air sample. In 3 patients a right atrial blood sample was collected, also, through a second catheter. In most patients two control measurements were made. An initial test dose of tolazoline hydrochloride (2 to 3 mg.) was then injected through the catheter and after a period of 1 to 3 minutes the tolazoline hydrochloride was administered in divided doses within a period of 10 to 15 minutes. A total dose of 25 to 60 mg./M.^{2} body surface was given in 2 or 3 divided doses into the pulmonary arterial or right atrial catheter. Pulmonary arterial and brachial arterial pressures were continuously recorded and, after 1 to 2 minutes, cardiac output was again determined.

In 2 patients skin temperature measurements of the toes and determination of finger blood flow by plethysmographic technique were made before and after tolazoline administration.

RESULTS

In 9 of the 10 patients a communication between the greater and lesser circulations was demonstrated by means of blood oxygen saturation measurements. Five patients had a left-to-right shunt at the ventricular level, 2 at the pulmonary level, and 2 at the atrial level. The other patient had no demonstrated shunt and was assumed to have primary pulmonary hypertension.

Pulmonary Arterial Pressure.—The control pulmonary arterial mean pressures were 50 to 100 per cent of the systemic arterial mean pressures, indicating a severe degree of pulmonary hypertension in all patients. Immediately following the injection of Priscoline there was a slight fall (5 to 10 mm. Hg) in pulmonary arterial pressure in some instances, lasting up to 15 to 30 seconds. The pressure returned to control levels and the final pressure response was not related to the initial effect. In 6 patients there was no significant change of pulmonary arterial mean pressure. Three patients showed a rise in mean pressure of 10 to 12 mm. Hg. Only one patient (Fig. 1) showed a fall of pulmonary arterial mean pressure of 15 to 20 mm. Hg.

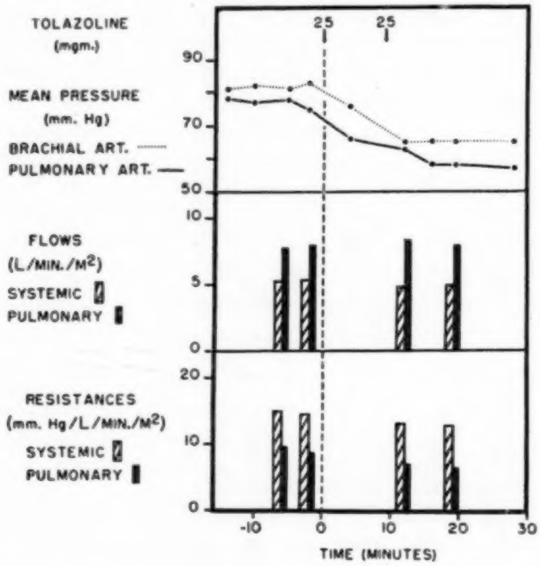

Fig. 1.—Patient A. L. Ventricular septal defect. Slight reduction in pulmonary and systemic vascular resistance, with decrease in pressures and increase of left-to-right shunt, following tolazoline administration.

Systemic Arterial Pressure.—Systemic arterial mean pressure changes after tolazoline paralleled the changes in pulmonary arterial mean pressure. There were no significant changes in the systemic arterial mean pressure in 6 patients; a slight rise was observed in 2, and a fall in 2 others. One patient who showed no significant changes in pulmonary arterial mean pressure had a reduction of mean systemic pressure of 15 to 25 mm. Hg (Fig. 2).

Pulmonary and Systemic Blood Flow.—The calculated flows have been related to body surface area in view of the wide variation in age of the patients studied.

The pulmonary blood flow was moderately elevated in 4 patients. The left-to-right shunts were, however, not large, and in none of the patients studied was pulmonary blood flow more than twice the systemic flow. Calculated pulmonary blood flow showed no significant changes after tolazoline administration in 6 patients, and a slight fall in 2 patients. There was an increase in pulmonary blood flow in 2 instances (12 and 20 per cent). In the 4 cases in which systemic blood flow was repeatedly measured there were no changes in 2, and a rise (10 and 25 per cent) in the other 2.

Pulmonary and Systemic Vascular Resistances.—The calculated pulmonary vascular resistance is possibly subject to considerable error in clinical studies in which pulmonary venous pressure cannot be measured. In this study, pulmonary wedge pressures were obtained in 5 patients, and did not deviate significantly from the normal either before or after tolazoline administration. However, in view of the problems inherent in the calculation of pulmonary vascular resistance, only major changes in pulmonary vascular resistance (greater than 2 mm. Hg/L./min.) were accepted as significant. Using these criteria, no significant changes in pulmonary resistance occurred in 6 patients, and there was a rise in 2 patients. Only 2 patients showed a significant drop in pulmonary vascular resistance of mild-to-moderate degree (12 and 25 per cent).

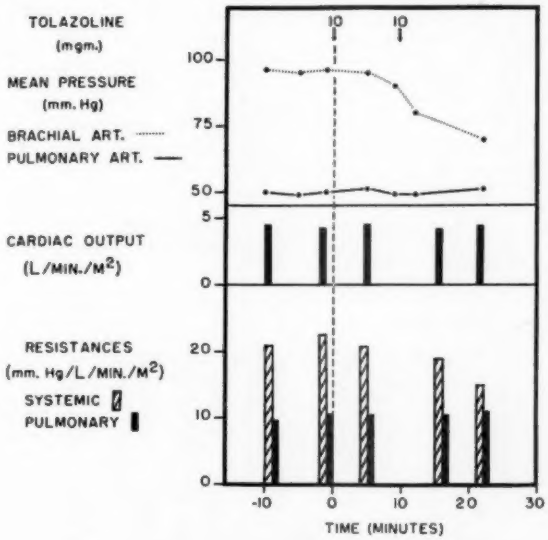

Fig. 2.—Patient L. Y. Primary pulmonary hypertension. No effect of tolazoline on pulmonary vascular resistance or pulmonary pressure. Definite reduction of systemic pressure and resistance.

Systemic vascular resistance showed a reduction after tolazoline administration in the 4 instances in which it was measured.

The patient with the largest decrease in pulmonary vascular resistance had a relatively smaller reduction of systemic resistance. The insertion of 2 catheters into this patient allowed for repeated simultaneous measurement of pulmonary and systemic flow. These studies showed an increase in left-to-right shunt due to greater reduction in pulmonary vascular resistance (Fig. 1).

TABLE I. EFFECT OF TOLAZOLINE HYDROCHLORIDE ON CARDIOVASCULAR DYNAMICS IN 10 PATIENTS

PATIENT	AGE	BSA	DIAGNOSIS		O_2 CONSUMPTION (ML./MIN./M.^{2})	A-V O_2		FLOWS (L./MIN./M.^{2})		PRESSURES (MM. HG)			RESISTANCES (MM. HG/L./MIN./M.^{2})		TOLAZOLINE DOSE
						P	S	Q_p	Q_s	PA MEAN	SA MEAN	PC MEAN	R_p	R_s	
1. S.B.	3 11/12	0.64	VSD	Control	164	2.9	4.6	5.7	3.6	63	75	6*	10.0		15 mg.
				20–23 min.	122	2.2		5.5		60	70		9.8		0–18 min.
2. R.C.	3 11/12	0.64	PDA	Control	160*	3.6	3.5	4.5	4.7	85	82	6	17.5		15 mg.
				18–21 min.		4.3		3.7		80	80	6	19.9		0–15 min.
3. M.D.	29	1.48	ASD	Control	153	3.6	5.5	4.2	2.8	55	78	5	11.6		50 mg.
				20–23 min.	135	3.9		3.5		67	85		17.4		0–15 min.
4. P.O.	9	1.25	ASD	Control	153	3.2		4.8		80	75	6*	15.7		25 mg.
				15–20 min.	148	3.2	5.1	4.6	2.9	78	73		15.8		0–5 min.
5. L.Y.	3 6/12	0.65	PPH	Control	170*	3.8		4.5	4.5	50	97	6*	9.8	21.0	10 mg.
						4.1		4.2	4.2	50	97		10.5	22.6	0–3 min.
				4–7 min.		3.8		4.5	4.5	52	95		10.2	20.6	10 mg.
				15–18 min.		4.2		4.1	4.1	49	80		10.5	19.0	10–15 min.
				20–23 min.		4.0		4.3	4.3	52	70		10.7	15.7	

6. J.M.	5	0.68	VSD	Control	210	2.6	5.0	8.1	4.1	80	78	5	9.2		15 mg. 0–15 min.
					202	2.6		7.8		80	84		9.5		
				15–18 min.	218	2.6		8.4		82	78		9.1		
				18–21 min.	210	2.6		8.1		82	78	6	9.4		
7. D.T.	3	0.61	VSD	Control	180*	3.0	3.8	6.0	4.7	69	76	5*	10.5		25 mg. 0–10 min. 10 mg. 16–18 min.
				12–16 min.		3.2		5.6		81	82		13.4		
				20–23 min.		3.0		6.0		76	78		11.7		
8. W.G.	15	1.4	VSD	Control	133	2.9	3.0	4.6	4.4	71	72	4	14.1	15.9	25 mg. 0–5 min. 25 mg. 12–15 min.
					138	3.2	3.5	4.4	3.9	71	72		14.7	17.6	
				8–11 min.	142	2.8	2.8	5.0	5.0	83	86		15.5	16.0	
				20–23 min.	140	2.8	2.8	5.0	5.0	83	81		15.5	15.7	
				23–26 min.	133	2.6	2.8	5.2	4.7	81	84	4	14.5	16.2	
9. K.C.	13 7/12	1.26	PDA	Control	138	3.3	4.8	4.2	2.9	79	79	6*	17.4	26.4	50 mg. 0–5 min.
					132	3.2	4.4	4.1	3.0	79	79		17.7	25.6	
				8–11 min.	131	2.7	3.7	4.9	3.6	81	84		15.3	22.7	
				12–15 min.	166	3.2	3.9	5.2	4.2	81	84		14.5	19.5	
10. A.L.	7 8/12	0.80	VSD	Control	184	2.4	3.5	7.7	5.3	78	81	5	9.5	14.9	50 mg. 0–9 min.
					181	2.3	3.3	7.9	5.5	75	83		8.8	14.7	
				10–13 min.	192	2.3	3.9	8.4	4.9	63	65		6.9	12.8	
				17–20 min.	196	2.5	3.9	7.8	5.0	58	65	4	6.7	12.6	

*Assumed value.

BSA—body surface area; PA—pulmonary artery; SA—systemic artery; PC—pulmonary capillary; Q_p—pulmonary flow; Q_s—systemic flow; R_p—pulmonary resistance; R_s—systemic resistance; A-V O_2—arteriovenous oxygen difference.

Peripheral Vasodilation.—All patients showed a flushing of the face and extremities, and the older individuals complained of a feeling of warmth. In 2 studies (Patients 8 and 9 in Table I) skin temperature measurements revealed a rise in temperature following tolazoline administration, suggesting a definite peripheral vasodilator effect (Fig. 3). This was further substantiated in 1 case (Patient 8) by the demonstration of a rise of finger blood flow from 3.4 to 9.2 ml./sec./mm.[3], as measured by plethysmography.

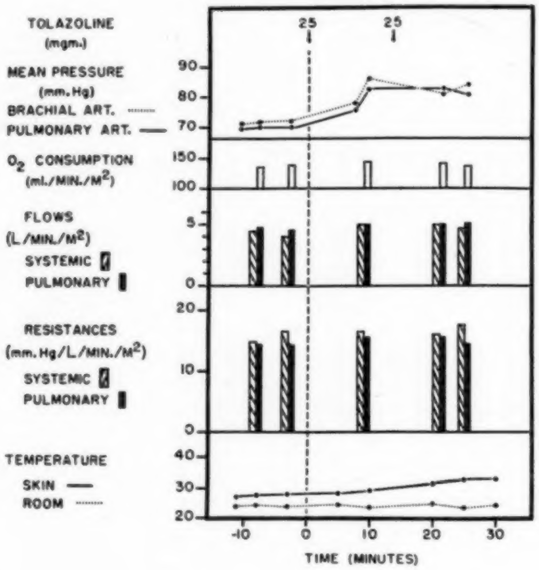

Fig. 3.—Patient W. G. Ventricular septal defect. No effect of tolazoline on pulmonary pressure or resistance. Skin temperature increased after tolazoline administration.

DISCUSSION

Tolazoline hydrochloride has been used extensively as a vasodilator in peripheral vascular disease.[5] It exerts a mild blocking effect, but also has a direct action in smooth muscle. Besides these effects, tolazoline also produces tachycardia and an increase in stroke volume in the intact animal, and the rise in cardiac output may be large enough to produce systemic arterial hypertension even though peripheral vasodilation is induced.[6] This complex action of tolazoline explains the variable responses of systemic arterial pressure observed in our patients. However, in all the cases in which systemic vascular resistance was measured, a definite decrease was noted following administration of the drug. Furthermore, vascular dilatation was demonstrated by skin temperature changes and finger blood flow measurement in these patients. It has been assumed, therefore, that in all instances a dose of tolazoline adequate to produce vasodilation was administered.

In contrast to the consistent reduction in systemic vascular resistance, pulmonary vascular resistance was reduced in only 2 of our 10 patients. The decrease in these 2 patients was of only moderate degree (12 and 25 per cent)

and the resistance was still markedly elevated above normal levels after the tolazoline administration. These findings conflict with those of Dresdale and associates,[1,4] who observed a significant decrease in pulmonary vascular resistance after tolazoline administration in several patients with primary pulmonary hypertension, and in some patients with emphysema. There are several possible explanations for these differences. One is that it is feasible that the premedication used conditioned the response to Priscoline. In our studies, two different types of medication were used, as described, and no difference in pulmonary vascular response was noted in the two groups.

An important consideration is the degree of vascular spasm associated with the pulmonary vascular obstruction. In patients with congenital heart disease with pulmonary hypertension, definite organic obstructive changes are usually noted in the small pulmonary vessels.[7,8] Since all but one of our studies were performed in patients with congenital heart disease with markedly elevated pulmonary vascular resistance, the possibility exists that vascular spasm played a minor role in the increased pulmonary vascular response, whereas in the group of patients studied by Dresdale it may have been a significant factor. We have observed, however, the effect of Priscoline in one patient with presumed primary pulmonary hypertension (Fig. 2); no significant reduction of pulmonary vascular resistance was noted.

Since tolazoline is not an effective drug in reducing pulmonary vascular resistance in congenital heart disease, even when administered intravenously, routine clinical therapy by oral administration cannot be recommended.

SUMMARY

The acute effects of intravenous administration of tolazoline hydrochloride on the cardiovascular dynamics have been studied in 10 patients with pulmonary arterial hypertension, all but 1 associated with congenital heart disease. Five patients had ventricular septal defects, 2 patent ductus arteriosus, 2 atrial septal defect, and 1 had no demonstrable cardiac lesion.

Pulmonary and systemic pressures and pulmonary blood flow were measured in all patients; and in 3 cases with left-to-right shunt simultaneous systemic blood flow measurement was obtained by insertion of a second cardiac catheter into the right atrium.

Systemic vascular effects of tolazoline were manifested by flushing of the skin, rise in measured skin temperature, increase in digital blood flow, and decrease in calculated systemic vascular resistance.

Pulmonary vascular resistance was not significantly affected in 9 patients. In 1 patient there was a moderate reduction of pulmonary resistance, with an increase in left-to-right shunt through a ventricular septal defect.

The effectiveness of tolazoline in reducing pulmonary vascular resistance as observed by other investigators could not be corroborated in our patients. The possibility is considered that the elevated pulmonary vascular resistance associated with congenital heart disease is due to organic changes, whereas in other diseases vascular spasm may have a significant role.

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A Case Report of Pulseless Disease in Turkey

Cavit Sökmen, M.D., Ankara, Turkey

Pulseless disease is characterized by the absence of pulsation in the carotid and radial arteries.[1] These findings are the result of thrombosis of the subclavian and carotid arteries secondary to a panarteritis of unknown etiology. Most of the cases described in the literature have been found in young women, although there is one report of its occurrence in a young male.[2] In 1908, Takayasu published his first case. Since that time there have been 68 cases recorded in Japan and 26 cases in Europe.[3]

CASE REPORT

A 30-year-old, married, white woman was admitted to the hospital on Aug. 14, 1957, with the chief complaints of weakness of the right arm, headache, fatigue, palpitation, blurred-vision, and syncopal attacks. Six months prior to her admission she developed deep aching in the region of the right shoulder and right side of the neck which lasted several days. From that time on she has had many attacks of this nature induced by mild work and subsiding on rest. Moderate exertion would further induce headache, palpitation, and syncopal attacks.

General physical examination revealed a well-developed, well-nourished white woman. The right radial, ulnar, and carotid artery pulsations could not be felt. Faint pulsations were noted in the region of the left carotid artery. Normal pulsations were present in the left radial artery, and bilaterally in the femoral, popliteal, dorsalis pedis, and posterior tibial arteries. Blood pressure could not be measured in the right arm, but was measured at 125/70 mm. Hg in the left arm and 160/70 mm. Hg in both legs. The nose and throat examination was negative and the lungs were clear to auscultation and percussion. The heart was normal in size to percussion, the rhythm was regular, the rate was 108 per minute, and no auscultatory abnormalities were noted. Auscultation in the right carotid area disclosed a faint systolic murmur.

Ophthalmoscopic examination disclosed a slight cataract formation in both eyes. The fundi were normal.

The neurological examination was negative, and there were no significant abnormalities in the remainder of the physical examination.

Laboratory studies included an erythrocyte count of 4,600,000 per cubic millimeter, and leukocyte count of 8,400 per cubic millimeter. The hemoglobin was 90 per cent by the Sahli method. The Schilling differential was normal, and erythrocyte sedimentation rate was 12 mm. in the first hour (Westergren method). Blood cholesterol was normal. Routine urinalysis was negative as were the Wassermann and the Kahn reactions, and the fasting blood sugar measured 93 mg. per 100 ml. By fluoroscopy and by chest film examination the size and configuration of the heart

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From the Department of Medicine, University Hospital, Ankara, Turkey.
Received for publication Oct. 24, 1957.

and aorta appeared to be normal, and the lung fields were clear. An electrocardiogram demonstrated the presence of sinus tachycardia with an auricular rate of 108. All of the conduction intervals were within normal limits.

COMMENT AND SUMMARY

The physical characteristics of pulseless disease are found in other aortic arch syndromes.[4] They may be caused by syphilitic arteritis, syphilitic aneurysm, dissecting aneurysm, and by traumatic injuries to the thorax. In the case presented there is no history, laboratory or x-ray findings suggestive of the other aortic arch syndromes. There is a history of visual disturbances and syncopal attacks. Objective abnormalities include the absence of arterial pulsation in the right arm and right carotid, absence of right arm blood pressure, and early cataract formation in the eyes. Because of these findings it is considered that the case is representative of pulseless disease.

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The Aortic Arch Syndrome of Takayasu

Chris L. Mengis, Captain, MC, USA, William Dubilier, M.D., and Kevin G. Barry, Major, MC, USA, New York, N.Y.

In 1908, Takayasu published his observations on the case of a young Japanese girl whose retinae manifested "strange anastomoses of the central vessels" in a wreath about the papillae, there being a gradual decrease of vision until she lost her sight from cataracts. Caccamise and Whitman,[4] in 1952, collected 58 cases from the Japanese literature, comprising bilateral loss of pulsations in the radial arteries, absence of detectable blood pressure in the arms, ocular findings including the progressive formation of peripapillary arteriovenous anastomoses and cataracts, visual disturbances ranging from photopsia and blurring of vision to blindness, and syncopal attacks frequently associated with convulsions and attributed to hypersensitivity of the carotid sinus. These authors presented a case report of their own, believing it to be the first from the occident. That same year, however, Skipper and Flint[12] reported 2 cases and reviewed 16 others collected from the occidental literature. In 1954, Ask-Upmark[2] published 2 new cases, with a comprehensive review of the literature, bringing to 28 the total number from the occident. Thirty-six of 44 Japanese cases in which age and sex were stated began under the age of 25 years, and of these 36 cases, 33 were female. Fifteen of the total 28 occidental cases began under age 25, all of them female. In the past two years, 3 more cases purporting to be Takayasu's disease have been reported in the occident. Because of the rarity of this syndrome and obscurity of its cause, it is deemed worth while to add another typical case.

CASE REPORT

A 35-year-old married Japanese woman was admitted to the U.S. Army Hospital, Fort Jay, on Oct. 12, 1956, because of a "blacking out" episode. The patient had been born in the seventh month of gestation, weighing 4 pounds at birth. Growth and development were normal, without unusual disease. Menarche occurred at 13 years of age, periods have been normal, but she has never conceived. When she was 14 years old, it was noted, on a routine examination, that she had no pulses in the upper extremities and apparently very low blood pressure in one arm. The severity of her condition is attested by the fact that during World War II she was given a special card indicating that, in the event of injury, pulse and blood pressure should not be used as an index of her condition. At age 16, the patient had a short-lived, severe dysentery. During the war years in Japan there was some weight loss associated with the restricted diet. At age 20,

Received for publication Nov. 6, 1957.

she was examined for acute trauma to the left eye and told that she had chronic eye disease unrelated to the trauma. At about this time she experienced difficulty in controlling her shears in her employment as a film-cutter. At age 30, the patient suffered her first episode of temporary loss of vision, several hours after slipping on some stairs. At age 33, while riding in a motor vehicle, she again had loss of vision lasting for about 15 minutes, and began having recurrent occipital headaches, which were considered at the time as psychogenic. At age 34, she first experienced a myalgic type of discomfort in the back and right hemithorax, which was relieved by change in position. The episode eventuating in hospital admission occurred when the patient experienced sudden onset of weakness, nausea, and blackout of vision while sitting at tea after several hours of sightseeing in New York. She lay down without immediate effect. After approximately 15 minutes her vision returned and she was asymptomatic. She was not wearing constrictive clothing about the neck at the time of the episode. No palpitation, chest discomfort, nor cyanosis have been noted with any of the episodes. The patient has never experienced claudication on mastication nor definite claudication of the upper extremities. There have been no visual symptoms other than the temporary amblyopia as noted above. There have been no symptoms of coronary or cardiac insufficiency.

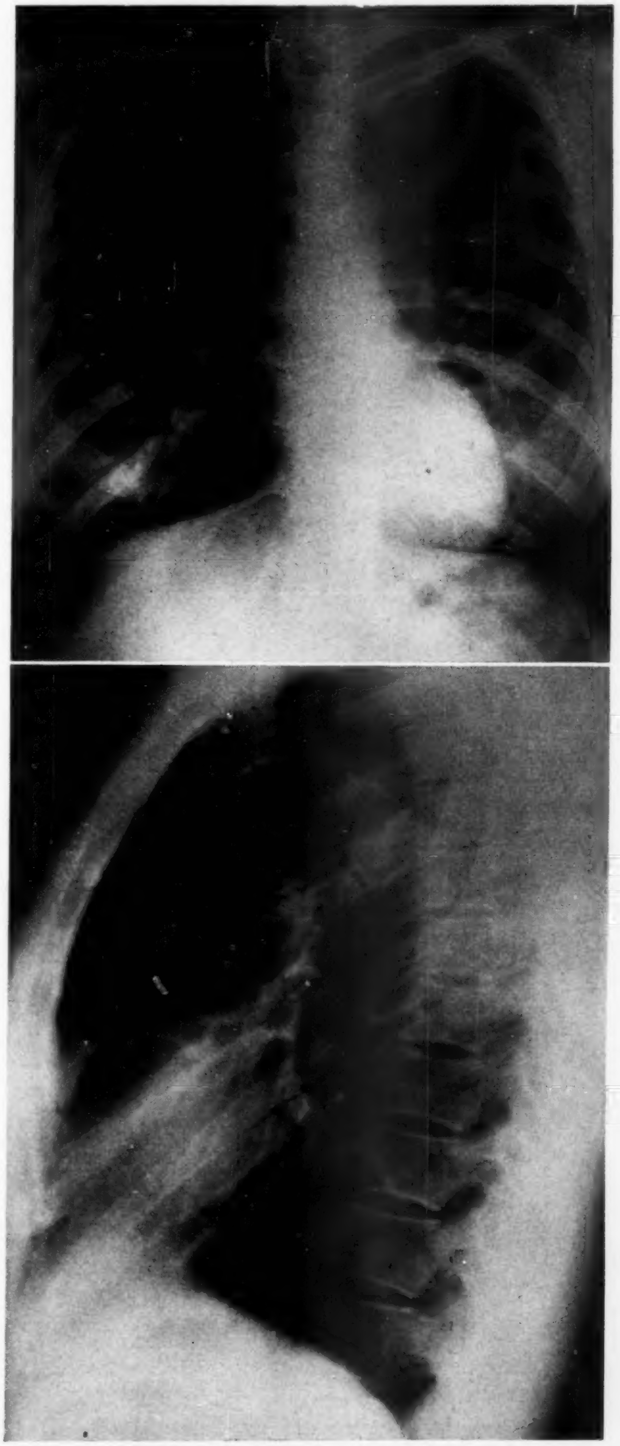
Physical examination revealed a small Japanese woman who was freckled but had no abnormal pigmentation. Mucous membranes were of good color. Fingernails were transiently cyanotic. Auscultation of the heart revealed a normal sinus rhythm with no murmurs or rubs. The heart tones were normal and the point of maximal impulse was in the fifth intercostal space at the midclavicular line. Lungs were clear to percussion and auscultation, but there was a bruit heard over the right lung posteriorly, along with a palpable thrill over the course of the intercostal arteries in that area. There was a very faint pulse in the right radial artery and no pulse in the left. Pulsations of the femoral, dorsalis pedis, and posterior tibial arteries were normal. Carotid pulsation was visible on the right but not on the left. Blood pressure was unobtainable in the left arm, 50/40 mm. Hg in the right arm, and 140/70 mm. Hg in the left leg. Temperature was normal, as was the pulse rate. The remainder of the physical examination was not remarkable. The nasal septum was intact.

Ophthalmological examination revealed a cataractous left lens which was subluxated into the vitreous; it was chalky white with crenated surface and torn zonule. The retina was not visible. There was a fine dust-like pigment on the rear surface of the cornea, marked atrophy of the iris, and a fixed irregular pupil 6 x 5 mm. Iridodonesis was not present. The right eye was normal throughout.

White blood count was 7,500 with 62 neutrophils, 37 lymphocytes, and 1 eosinophil. The hematocrit was 40, hemoglobin 14.2 Gm., sedimentation rate (Wintrobe) 2 mm. per hour. Urinalysis revealed a specific gravity of 1.025, with negative albumin, trace of sugar, and normal sediment. Repeat urinalysis before and after a meal was negative for sugar. Fasting blood sugar (Folin-Wu) was 100 mg. per cent, with a 2-hour postprandial value of 120 mg. per cent. Cardiolipin microflocculation was negative. Total protein was 7.2 Gm. per cent, with 4.2 Gm. albumin and 3 Gm. globulin. Blood cholesterol was 245 mg. per cent, and total lipids 1,295 mg. per cent. Serum calcium was 9.6 mg. per cent, inorganic phosphorus 3.5 mg. per cent, alkaline phosphatase 4.5 Bodansky units. Serum electrophoresis revealed normal protein fractions. Antistreptolysin-O titer was 100 to 150 units. Blood Buffy coat contained no lupus erythematosus cells.

Electrocardiogram was interpreted as borderline because of a wide estimated ventricular gradient and precordial T-wave inversion from V_2 to V_4. X-rays of the chest (Fig. 1) in the posteroanterior and lateral views revealed calcification of the superior margin of the aortic arch; the aorta was slightly tortuous. Notching of the ribs on the right side was also seen. Fluoroscopy of the heart suggested minimal left ventricular hypertrophy. X-rays of the skull and left orbit were normal, there being no radiopaque foreign bodies in the latter area. There was some spur formation in the cervical spine at C_6 and C_7 anteriorly, and some narrowing of the disc space between these vertebrae. Slight kyphosis was present at C_4, C_5, and C_6. X-rays of the abdomen and the extremities revealed no evidence of vascular or other pathologic calcification. Lateral views of the chest offered no evidence of enlargement of the internal mammary arteries. Electroencephalogram was interpreted as normal.

Carotid and upper extremity pulse tracings were flattened compared to those of the lower extremities.

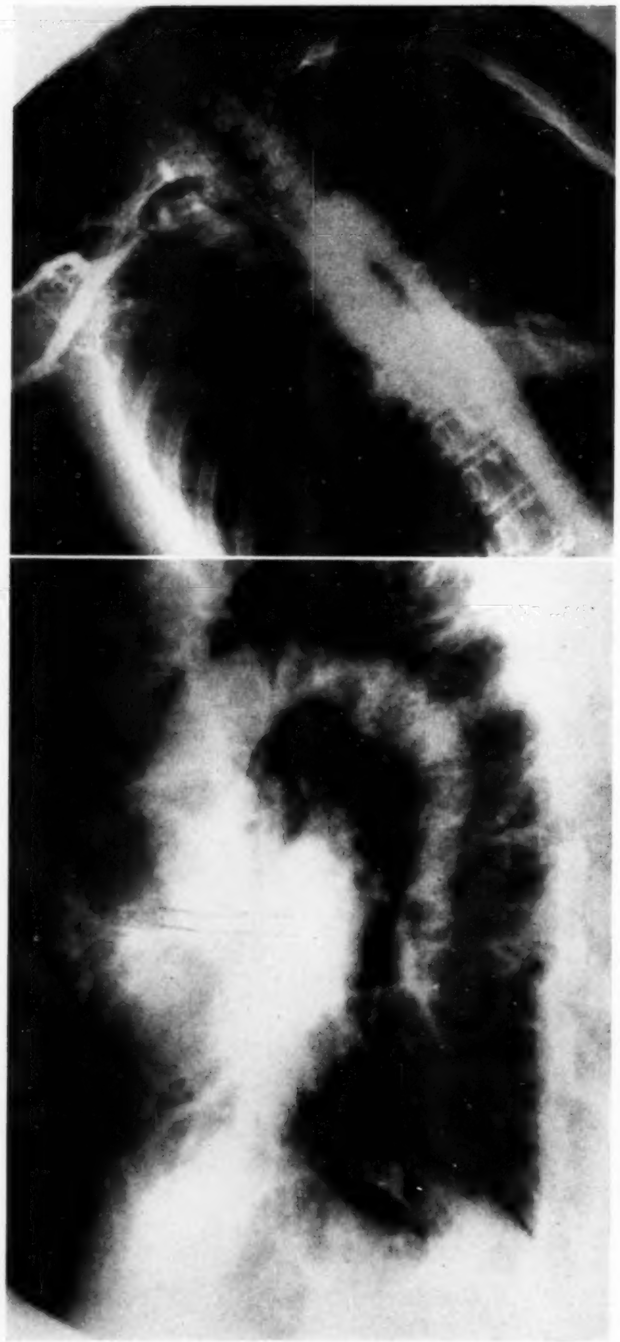


A.

B.

Fig. 1.—Posteroanterior (*A*) and lateral (*B*) chest films demonstrating notching of the right lower ribs and calcification in the aortic arch. The cardiac size and contour appear normal.

A.



B.

Fig. 2.—Posteroanterior (A) and lateral (B) angiocardiograms with opacification of the aorta. There is slight narrowing of the lumen and variations in the contour of the aortic arch and upper descending aorta.

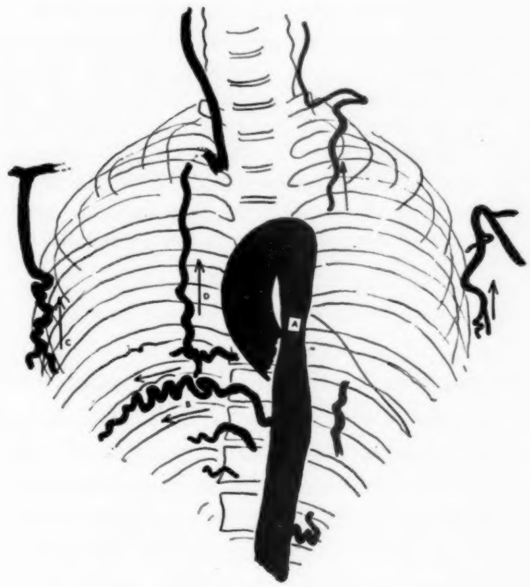


Fig. 3.—Composition tracing of Fig. 2,*A* and subsequent serial angiocardiograms, demonstrating progressive opacification of large tortuous intercostal arteries (*B*), lateral thoracic arteries (*C*), and internal mammary arteries (*D*) which lead into the axillary and carotid arteries. Arrows indicate direction of blood flow.

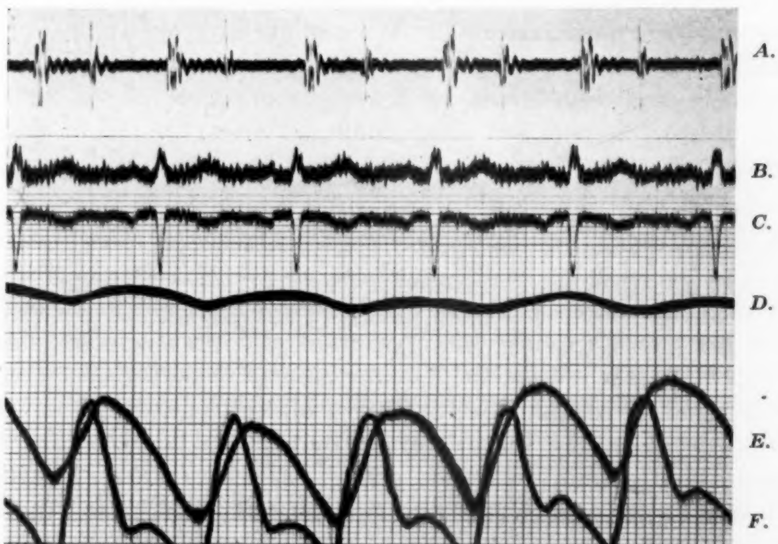


Fig. 4.—Peripheral arterial pulse tracings, with marked diminution of amplitude in the carotid arteries and slight damping in the arms. Arm and leg tracings were equal bilaterally. *A*, Sound. *B*, Lead I. *C*, Lead aV_R. *D*, Neck. *E*, Arm. *F*, Leg.

Serial *angiocardiography* was done to visualize the brachiocephalic vessels and to trace the course of circulation (Fig. 2). This procedure demonstrated irregularity of the contour and slight narrowing of the lumen of the aortic arch and descending aorta. There was no opacification of the proximal segments of the innominate, left common carotid, or left subclavian arteries. This suggested occlusion of these vessels at their origins in the aortic arch. However, with opacification of the descending aorta, there was demonstrated large tortuous intercostal arteries along the lower ribs, especially on the right, where they corresponded to the rib notches and bruits. Subsequent serial films demonstrated reversal of the usual blood flow from the intercostal arteries, through the internal mammary, lateral thoracic, and other major vessels of the thoracic wall into the axillary and carotid arteries (Fig. 3).

DISCUSSION

The finding of bilaterally absent radial pulsations in a young woman with signs and symptoms of ocular and cerebral ischemia and progressively severe changes in the lens and retina, accompanied by signs of collateral circulation to the head and arms via the intercostals, internal mammaries, and long thoracic arteries, suggests the presence of the aortic arch syndrome of Takayasu, variously called "pulseless disease" or "reverse coarctation." It is felt that this entity may justifiably be grouped separately from the similar syndrome caused by syphilitic aortitis and by degenerative vascular disease in the elderly, on the grounds of consistently negative clinical and serologic evidence of syphilis and, in the latter case, of dissimilar histopathology and the rarity of advanced atherosclerosis in this female age group.

Takayasu's syndrome is ascribed to a degenerative arteritis of the aortic arch and brachiocephalic trunks, with obliteration of the lumina of the latter by an intimal cushion and organized thrombus. The process has been described as involving the aortic arch, the ascending and descending aorta, the innominate artery, the subclavian arteries as far as the origin of the vertebral arteries (and indeed into the brachial arteries), and the carotid arteries as far as the skull. It should be remembered, however, that numerous cases of similar arteritis involving the cerebral arteries and other smaller arteries throughout the body have been reported. Takayasu's disease may be a variant of such idiopathic arteritis, with a predilection for the vessels arising from the aortic arch.

Of the six autopsy protocols which we have reviewed, two[7,9] suggest intimal atheroma and arteriosclerosis as causative pathology, whereas the other four describe a degenerative vasculitis in which the adventitia is hardened and thickened, with endarteritis of the vasa vasorum and perivascular infiltrations of lymphocytes and plasma cells.[3,5,6] The media manifests disruption of the elastic lamellae by collagenous connective tissue and infiltrations of plasma cells, lymphocytes, and giant cells. In the case reported by Beneke,[6] medial muscle fibers were necrotic and atrophic in some areas. The intima is almost universally described as sclerotic and thickened, containing cells with fat droplets, and in the more advanced cases it is densely fibrotic and specked with fine deposits of calcium. This would explain the aortic calcifications on the radiographs of the present case. However, calcification of this degree is probably an unusual feature. Demarcation between intima and media is difficult.[3] Lumina of the brachiocephalic trunks are filled with organized thrombi.

Secondary changes reported, in addition to the rich collateral circulation, have been dilation of the retinal arteries with profuse peripapillary anastomoses and microaneurysms, lens cataracts, iris atrophy, glaucoma, atrophy of the alveolar processes with loss of teeth, and perforation of the nasal septum.

Ask-Upmark, noting the large incidence in females of the sexually active age group, and because the sedimentation rate was reported to be increased in 13 of his 28 cases, views as the most likely etiology a collagenous disease akin to lupus erythematosus. Although there was no evidence of active inflammation in our patient, she might represent a case which has "burned out." Trias de Bes and associates,[13] in an eye enucleated because of glaucoma in a young female with typical findings of Takayasu's disease, noted a pellicle over the retina and an optic papilla containing starred mesenchymal and fusiform or lymphoid cells; they postulated that the vascular changes might also be on a dysontogenetic basis. The premature birth of our patient lends support to this suggestion.

Efforts to implicate various infectious, inflammatory, and degenerative processes have thus far been unsuccessful. Tuberculosis has been mentioned by Japanese authors as possibly implicated, because of the finding of giant cells in the involved vessel walls. In our case the blood cholesterol and total lipid levels are in the upper normal limits.

Symptoms are produced by ischemia of organs supplied by the involved brachiocephalic vessels and are primarily cerebral and ocular. Syncope is common, and has in some cases been ascribed to increased sensitivity of the carotid sinus, being touched off by turning the head to one side or the other. Visual blackouts, or "visual claudication," probably are even more frequent. Neurological complications, hemipareses, or paralyses, and convulsions have been noted. Masticatory claudication and claudication of the arms are apparently more uncommon. The clinical picture of diminished blood flow and eye changes is directly attributable to brachiocephalic occlusion leading to rest or demand ischemia. The thoracic bruits, rib notching, and chest discomfort are attributable to the collateral circulation which is analogous anatomically to the collateral circulation of coarctation in which the direction of flow has been reversed. Fingernail cyanosis is probably due to stasis.

Tachycardia and arterial hypertension are measured in the thighs, and occasional cardiomegaly may be secondary to a physiologic response of the carotid receptors and an attempt to increase blood flow through the involved vessels. Clinical confirmation of obstruction of the brachiocephalic vessels can be obtained through the use of angiocardiography.

Although all cases of Takayasu's syndrome appear progressive and are presumably fatal, it should be remembered that only 7 necropsies have been reported in the occident.

Numerous means of treatment have been suggested. Ask-Upmark stresses that it is of paramount importance not to overstress the ischemic structures. ACTH and cortisone have been tried in a few cases, with indecisive results. Vasodilating agents present an obvious hazard, although alcohol may be of some benefit. Anticoagulants have been suggested, but we are not familiar with a case in which they have been used. Digitalis should be used with caution in

cases of hypersensitive carotid sinus. It should be borne in mind when contemplating the use of atropine for carotid sinus syncope that glaucoma is a frequent complication. Suggested surgery has included thrombectomy of involved vessels, denervation of the hypersensitive carotid sinus, sympathectomy, and removal of cataracts. The last procedure should also be viewed with reserve, as the retinal changes may antedate opacification of the lens. It would appear to the authors that the only reasonably successful approach would be through reconstructive vascular surgery.

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Aortic Arch Syndrome

Fay Segal, M.D., and A. Berezowski, M.B., B.Ch., D.M.R.D., R.C.P. & S. (Eng.)
Johannesburg, South Africa

The clinical syndrome characterized by absence of pulsation in the arteries arising from the arch of the aorta has aroused considerable interest in recent years.[1-3] Frovig,[4] in 1946, first suggested the name "aortic arch syndrome." Other terms which have been applied to pulse abnormalities of this type are "reverse coarctation," "chronic subclavian-carotid obstruction syndrome," "Takayasu's disease" and "pulseless disease."

A large variety of pathologic lesions may be responsible for such arterial occlusion. The most common cause appears to be an arteritis of unknown origin which occurs most frequently in young women.[5] Other possible etiological factors are syphilitic aortitis and arteritis with or without aneurysm formation, atheromatosis, giant cell arteritis, chronic dissecting aneurysm, chest trauma, congenital anomalies, mediastinal tumors, and thrombophilia.[2]

The following is the report of a case believed to be due to syphilitic arteritis.

CASE REPORT

An African woman, aged 49 years, was admitted to Baragwanath Hospital on Feb. 17, 1957. She was aphasic and mentally confused. According to her husband she had experienced recurrent attacks of weakness of the right arm and leg for 2 years. These episodes lasted from about 24 to 48 hours. Recovery was rapid but mild weakness persisted in the intervals between attacks. Three weeks before admission to hospital sudden deterioration developed and she became completely paralyzed and unable to speak coherently.

Past History.—She complained of recurrent generalized headaches and blurring of vision of both eyes for a number of years. Apart from occasional mild "dizzy spells" she had not experienced any syncopal or epileptiform seizures. Three years previously she had been treated at another hospital for pulmonary tuberculosis.

Examination.—She was a well-nourished woman, but her face appeared thin and drawn. She was afebrile. The radial pulses were barely palpable, the right being weaker than the left. Pulsations in the brachial and right carotid arteries were diminished but no pulsation could be felt along the course of the left common carotid artery and its branches. A marked systolic thrill and murmur were present in the suprasternal notch and lower half of the right side of the neck. The femoral and pedal pulses were bounding in character. Pistol-shot sounds were audible.

From the Departments of Medicine and Radiology, Baragwanath Hospital, Johannesburg, South Africa.

Received for publication Nov. 23, 1957.

The heart was slightly enlarged, the impulse at the apex indicating left ventricular hypertrophy. Blowing systolic and diastolic murmurs were heard in the aortic area with radiation down the left sternal border. There were no signs of cardiac failure. The blood pressure in the right arm was 80/60 mm. Hg, and 95/55 mm. Hg in the left arm. In the lower extremities the pressures as measured by leg cuff were 170/60 mm. Hg in the left leg and 160/60 mm. Hg in the right leg.

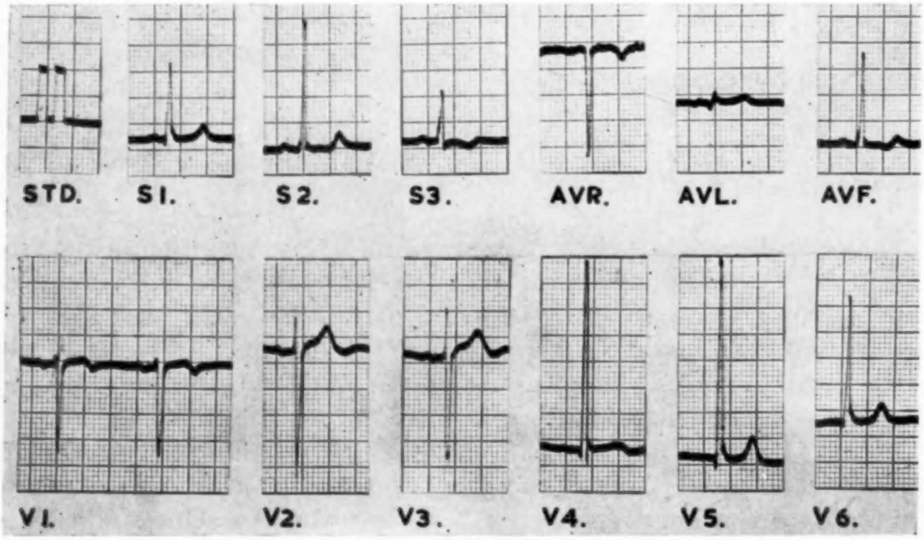

Fig. 1.—Electrocardiogram showing left ventricular hypertrophy.

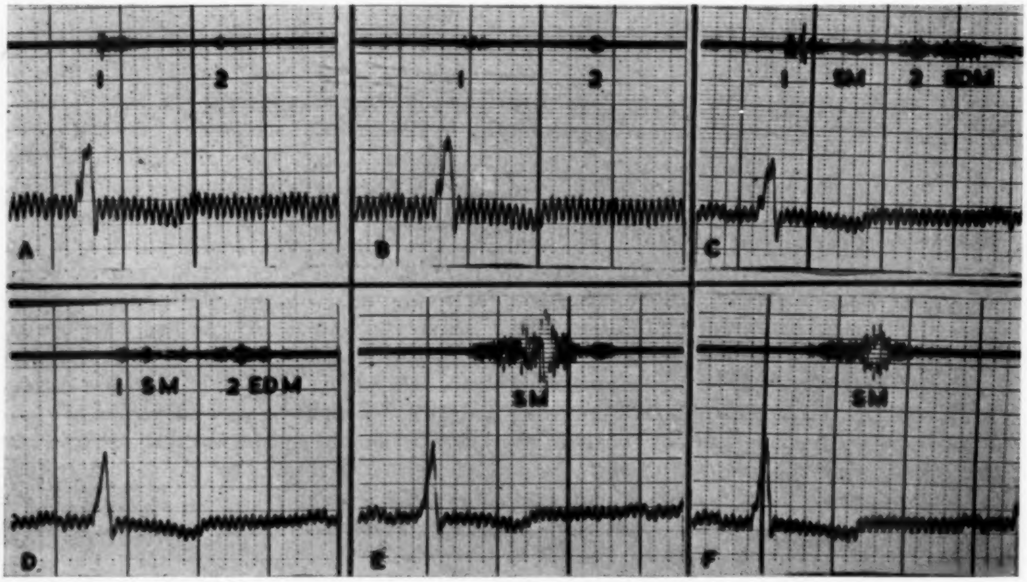

Fig. 2.—Phonocardiogram with electrocardiogram (standard Lead II). *SM* = Systolic murmur. *EDM* = Early diastolic murmur. *A*, At the apex. *B*, At the left sternal border in the fourth intercostal space. *C*, At the pulmonary area. *D*, At the aortic area. *E*, At the right infraclavicular region. *F*, Over the right common carotid artery.

Neurological examination revealed a right-sided, flaccid hemiplegia, hypoesthesia, and hemianopia. The tendon reflexes were increased on the right. The plantar responses were flexor. The optic fundi were normal.

Laboratory Investigations.—Hemoglobin was 10.5 Gm. per 100 ml.; white blood cells, 4,900 per cubic millimeter; differential count, normal; erthyrocyte sedimentation rate, 33 mm. per hour (Wintrobe); urinalysis, normal; blood cultures, negative; blood lipids, normal. The Wassermann, Kahn, Kolmer, and Eagle tests were strongly positive. *Treponema pallidum* immobilization test was 100 per cent positive. The cerebrospinal fluid was normal. Kolmer cardiolipin Wassermann and Lange's colloidal gold tests were negative.

The electrocardiogram (Fig. 1) showed left ventricular hypertrophy. The phonocardiogram (Fig. 2) confirmed the auscultatory findings.

Radiologic Examination.—The posteroanterior view of the chest (Fig. 3) showed a mild mid-dorsal scoliosis convex to the right. There were .5 to 1 cm. opacities poorly defined in both upper and right mid-zones and pleural thickening at the left apex. The findings were consistent with tuberculous infection but the activity of the disease was uncertain at a single examination.

The heart was enlarged in its transverse diameter, the cardio-thoracic ratio being 12:23. There was mild unfolding of the aorta.

Fluoroscopy revealed normal pulsations of the heart and aorta with moderate enlargement of the left ventricle. No aneurysmal dilatation or calcification could be seen in the aorta.

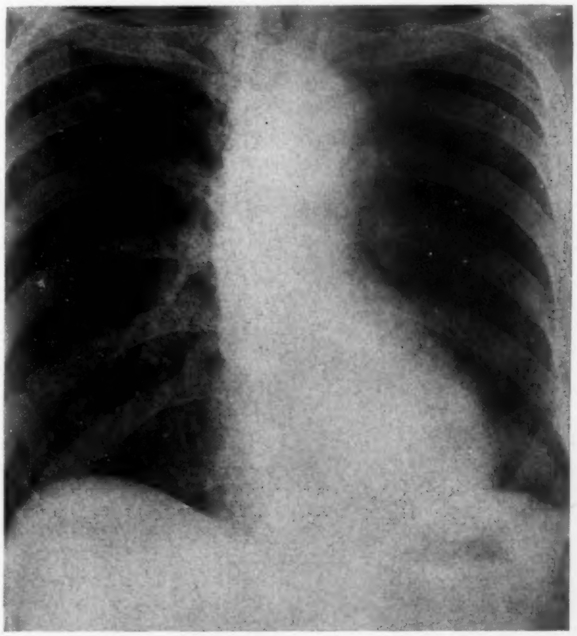

Fig. 3.—Posteroanterior view of chest.

Aortography (*Fig. 4*).—The left femoral artery was punctured under local anesthesia and, using the Seldinger technique,[18] a PE 205 catheter was inserted percutaneously and passed into the ascending aorta. Twenty-five c.c. of 70 per cent diodone was injected manually. Three films were obtained in rapid succession using the lateral component of a Schonander serial changer usually employed in cerebral angiography.

No abnormality was noted in the ascending aorta. There was well-marked stenosis of the commencement of the innominate artery for a distance of approximately 3 mm., with poststenotic dilatation of the artery distal to this. The right common carotid and its branches (*A* in Fig. 5) and the right subclavian arteries were normally visualized. There was nonfilling of the right vertebral artery.

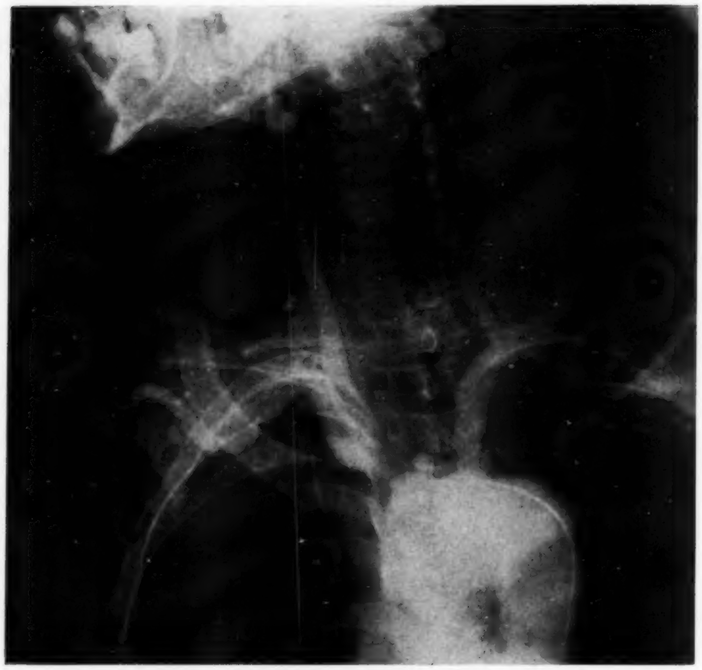

Fig. 4.—Aortogram showing the stenosed and occluded vessels arising from the aortic arch.

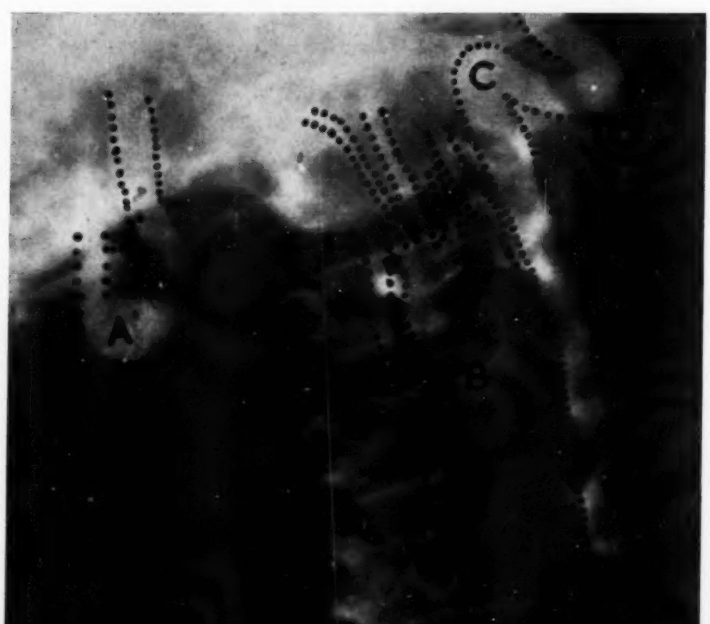

Fig. 5.—Retouched enlargement demonstrating the reopacification of the left common carotid artery. *A*, Right common carotid artery. *B*, Left common carotid artery. *C*, Left vertebral artery.

The left common carotid terminated abruptly at approximately 1 cm. distal to its origin from the arch of the aorta. It was seen to reopacify faintly at the level of the carotid sinus (*B* in Fig. 5). This was achieved by means of collateral vessels from the right external carotid circulation and branches of the inferior thyroid artery on the left side. The internal carotid artery so visualized was of narrow caliber.

The left subclavian artery showed narrowing at its commencement for a distance of approximately 4 mm. (Fig. 4), and, distal to this, mild poststenotic dilatation. The left vertebral artery was well opacified and its caliber was larger than normal (*C* in Fig. 5).

Progress and Treatment.—The patient improved rapidly with bed rest and physiotherapy. Within a few days speech returned, hemianopia and hypoesthesia cleared, but slight motor weakness persisted. No improvement was observed in the pulses of the neck and upper extremities, and the blood pressures remained unchanged.

Antisyphilitic treatment was begun when she was already ambulant. Oral potassium iodide and bismuth injections were administered initially, followed by a course of 12 million units of penicillin. Cortisone was used to prevent a possible Herxheimer reaction.

Since discharge from hospital she has been seen regularly at the outpatient department. There has been no change in her condition.

DISCUSSION

The clinical picture of recurrent episodes of hemiparesis due to occlusion of the internal carotid artery is a well recognized syndrome.[6] While the cerebral manifestations in this patient were undoubtedly due to involvement of the left carotid artery, the presence of diminished pulses in the upper extremities indicated that the pathologic process involved other branches of the aortic arch. In support of this was the finding of hypotension in the upper limbs with normal or slightly raised blood pressure in the legs.

The systolic murmur and thrill at the root of the neck, associated with aortic incompetence, suggested an alternative diagnosis of aortic stenosis, complicated by subacute bacterial endocarditis with emboli. This appeared unlikely in view of the absence of the usual features of bacterial endocarditis and the negative blood cultures. The bruit was considered to be due rather to partial occlusion or stenosis of the innominate or carotid arteries and has been frequently described in such conditions.[7] A continuous systolic and diastolic murmur has also been reported in a number of cases.[8]

The clinical manifestations of the aortic arch syndrome are well defined and have been reviewed by Skipper and Flint,[1] Ross and McKusick,[2] and Currier and associates.[9] The predominant symptoms are cerebral and visual, and include syncopal attacks (sometimes associated with hypersensitivity of the carotid sinus). At times, convulsions, hemiplegia or death from cerebral softening may occur.

The ophthalmological disturbances described are repeated blurring of vision, progressive deterioration in sight, cataracts, and retinal changes which include aneurysmal dilatations and arteriovenous communications of retinal vessels. In addition, atrophy of the iris and optic nerve, corneal opacities, retinal pigmentation, and atrophy have also been reported.

Facial hemiatrophy and atrophy of the facial bones, perforation of the nasal septum, collapse of the nasal bridge, and trophic changes have been ascribed to diminished arterial circulation.[2,10] Claudication of the masseter muscles occurs rarely.

Evidence of a collateral circulation is shown sometimes by the presence of prominently dilated vessels over the chest and abdomen, and crenations of the rib margins. Trophic skin changes in the upper extremities are rare, but clubbing, cyanosis, fatigue, pain or claudication have been reported.[3]

Confirmatory evidence of the site and extent of the arterial disease can be satisfactorily demonstrated only by aortography. This anatomic demonstration is, furthermore, of considerable importance when surgical treatment by arterial grafting is contemplated.

Angiocardiography has proved disappointing where adequate opacification of the arch and its branches is required. Many different techniques of aortography have been introduced by various workers.[11-17] Most of these methods cannot be safely employed where the common carotid and subclavian arteries are partially or totally occluded. The method of choice in these cases appears to be the percutaneous insertion of a catheter through a femoral artery into the ascending aorta, using the Seldinger technique.[18]

The etiology in our case was considered to be syphilitic arteritis, in view of the strongly positive serologic and *Treponema pallidum* immobilization tests.

Pathologically, syphilis may cause occlusion by involvement of the ostia of the branches of the aortic arch, or by thrombosis which may complicate aneurysmal formation of the aortic arch or form within the branches. In some instances syphilitic changes have been demonstrated in the proximal portions of the great arteries for a variable distance.[1] Syphilitic infection may also predispose to the development of local atheromatosis, and this combination has been suggested as a cause in some cases.

It is unlikely that in this case pulmonary tuberculosis (probably inactive) was of any etiological significance. Tuberculosis was thought to be responsible in some of the cases reported from Japan.[19] This, however, has not been confirmed by other workers.

SUMMARY

1. A case of aortic arch syndrome is described. The etiology is considered to be syphilitic arteritis.

2. The presenting symptoms were cerebral and due to occlusion of the common carotid artery. The stenosed and occluded vessels were demonstrated by aortography.

3. The clinical features of the syndrome are discussed.

We wish to thank Mr. C. Shevitz for the photographs, and Dr. V. Wilson, Senior Physician, Dr. H. Clain, Senior Radiologist, and Dr. I. Frack, Superintendent, Baragwanath Hospital, for permission to report this case.

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Tricuspid Atresia With Right Axis Deviation: Case Report and Review

John J. Sullivan, Jr., M.D., and Joseph L. Mangiardi, M.D., Roslyn, N. Y.

Tricuspid atresia accounts for about 3 per cent of all cases of cyanotic congenital heart disease.[1] Prior to the advent of surgical treatment for these conditions, their diagnosis and classification were largely matters of academic interest. However, since the development and standardization of the Blalock and Potts procedures and with the more recent use of open cardiac surgery for definitive correction, the necessity for more exact knowledge of the morbid anatomy and pathologic physiology in each case has become manifest.

The purpose of this communication is presentation of a case of tricuspid valve atresia with right axis deviation on the electrocardiogram, and a brief review of the published cases of this anomaly which have been proved by necropsy.

CASE REPORT

J. O., a 3-month-old white male, was admitted to the hospital on Jan. 31, 1956, with a history of cyanosis since birth. At 6 weeks of age the infant had been hospitalized and treated elsewhere for "pneumonia." Because of the persistent cyanosis and a loud precordial murmur, congenital heart disease was suspected, and he was transferred to St. Francis Hospital.

Examination on admission revealed an underdeveloped cyanotic infant, weighing 10 pounds. There was slight distention of the neck veins and moderate pitting edema of the extremities. A slight left precordial bulge was noted, and sinus tachycardia (rate 100) was present. Auscultation revealed a Grade 2 systolic murmur, loudest at the left sternal border. The lung fields were clear. The liver edge was palpable 3 fingerbreadths below the right costal margin but did not pulsate.

Roentgenograms of the chest revealed a markedly enlarged heart with increased pulmonary vascularity (Fig. 1). Angiocardiograms demonstrated a right-to-left interatrial shunt and a single opacified ventricle.

An electrocardiogram (Fig. 2) showed right axis deviation (102°), vertical heart position, and biphasic ventricular complexes from V_4R to V_6. Peaked P waves were present in V_2 and V_3.

Laboratory Data.—Hematologic findings were normal. Urinalysis revealed 2 plus albuminuria.

Course.—A diagnosis was made of congenital heart disease of the cyanotic type, possible single ventricle, with congestive failure. The infant was placed in an oxygen tent, rapidly digitalized, and given Mercuhydrin. No improvement was noted, and he expired on the second hospital day.

Pathologic Findings.—The heart weighed 30 grams. The right atrium was dilated, and its floor exhibited an imperforate dimple at the site of atresia of the tricuspid valve leaflets. The foramen ovale (Fig. 3) measured 1 x 2 cm. The left ventricle measured 10 mm. in thickness. Its

From the Department of Surgery, St. Francis Hospital, Roslyn, N. Y.
Received for publication Sept. 23, 1957.

Fig. 1.—Posteroanterior chest film showing massive cardiomegaly with dilated right atrium and increased pulmonary vascularity.

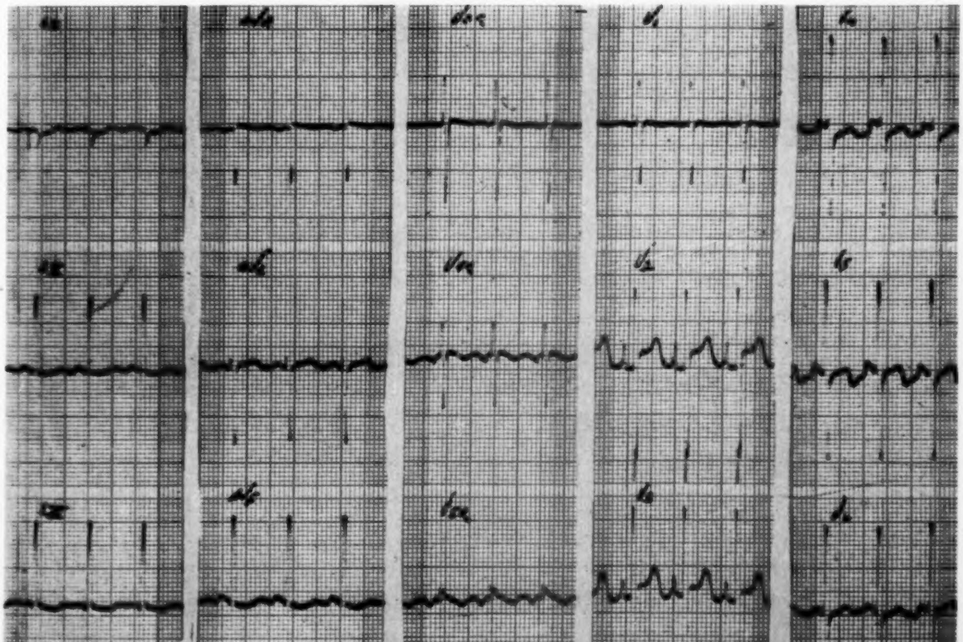

Fig. 2.—ECG showing right axis deviation, vertical heart, and almost equiphasic complexes in most precordial leads. V_7 and V_8 should have been taken. Note peaked P waves in V_2-V_3.

outflow tract led to a normal pulmonary valve and large pulmonary artery. A diminutive right ventricle with hypertrophic wall measuring 9 mm. in thickness was situated anteriorly (Fig. 3). The interventricular septum was deficient, being composed of a hypoplastic conus ridge. Anteriorly, a hypoplastic aorta arose from the right ventricle. The ductus arteriosus was probe-patent. The lungs and abdominal viscera showed marked congestion.

In summary, tricuspid atresia, transposition, diminutive right ventricle, and notable absence of obstruction to pulmonary flow were present, placing this heart in Class IIB (vide infra).

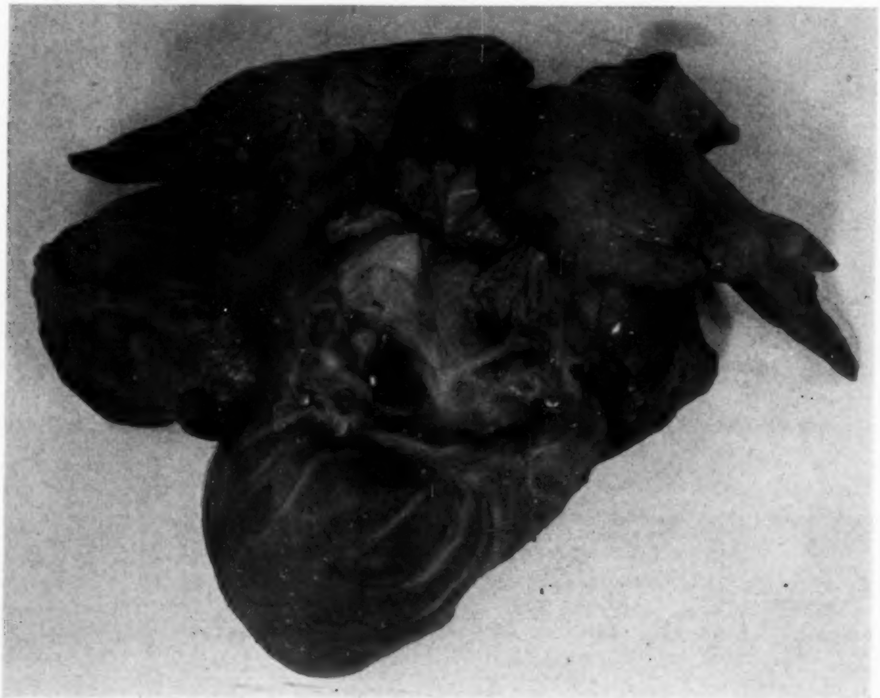

Fig. 3.—The heart and attached lungs. Note the patent foramen ovale, seen from right side. The dimple is barely visible on the atrial floor. The large LV, unopened, is below, and the small RV is seen at the right.

REVIEW

In 1949, Edwards and Burchell[2] collected 45 autopsy-proved cases of tricuspid atresia and suggested a classification. We were able to find 98 additional cases[3-24] in which the published data were of sufficient clarity for verification of the diagnosis and classification of the type. The total of 143 reported cases are classified in Table I. The pathologic findings were quite uniform within each group. All hearts were slightly to markedly enlarged; there was hypertrophy of the left ventricle in each case. Atresia of the tricuspid orifice and patency of the foramen ovale, or, less commonly, a true defect of the atrial septum, were always found. The atria were usually dilated and hypertrophied, especially the right.

The hearts in Type I (Table I) showed the great arteries to be normally situated. In Subtype A the pulmonary trunk was atretic and the ventricular

septum was usually intact, the right ventricle being defunctionalized. Subtype I-B, the most frequently encountered form, showed stenosis of the pulmonary artery or valve, or "subpulmonary stenosis," the latter manifested by narrowing of the right ventricular outflow tract. The ventricular septum was always deficient, allowing blood to reach the lungs by way of the pulmonary trunk.

Type II hearts (Table I) were those in which the great arteries were transposed. These cases were in the minority, in contrast to cases of single ventricle where transposition is the rule. All showed valvular or subvalvular obstruction to pulmonary flow. It is this subtype (II-A) which is usually associated with the greatest longevity.

TABLE I. CLASSIFICATION OF 144 REPORTED CASES OF TRICUSPID ATRESIA PROVED BY AUTOPSY (MODIFIED FROM EDWARDS AND BURCHELL)

			Number of Cases
Type I:	Tricuspid atresia without transposition of great vessels		107
	A. Pulmonary atresia; usually closed ventricular septum	17	
	B. Pulmonary or subpulmonary stenosis	86	
	C. No pulmonary or subpulmonary stenosis	4	
Type II:	Tricuspid atresia with transposition of great vessels		37
	A. Pulmonary or subpulmonary stenosis	23	
	B. No pulmonary or subpulmonary stenosis	14	

Hearts classified as Subtype II-B showed no anatomic evidence of obstruction to pulmonary flow. The ventricular septum was patent and poorly developed. This group of cases and those of Type I-A are not amenable to a shunt operation, while the other types can be so treated.

Ages at the time of death in these patients with tricuspid atresia varied from a few hours to 56 years. Of 90 cases in which the age of demise was given, 70 succumbed before the second birthday. The average age of death in this group was 7 months. Sex distribution was about equal.

Clinical findings were characteristic of cyanotic congenital heart disease in general and consisted of cyanosis, failure to gain weight properly, dyspnea, and a left precordial systolic murmur.

The roentgenographic features varied somewhat, depending upon the magnitude of pulmonary blood flow. Chest films of Types I-A, I-B, and II-A revealed a slightly enlarged heart with diminished pulmonary vascularity. Type II-B cases, with no obstruction to pulmonary flow, revealed a markedly enlarged heart and increased pulmonary vascularity, as in our case.

Angiocardiograms showed direct filling of the left atrium from the right atrium. Astley,[5] Cooley,[8] and Campbell[27] each has summarized the merits of this study in these cases.

Electrocardiography has long been one of the principal diagnostic tools in tricuspid atresia, because, unlike in most other cyanotic congenital heart conditions, it usually reveals left axis deviation. In recent years a number of cases

with QRS axis within the normal range have appeared. Ebel,[9] Kroop,[15] Astley,[5] and Neill[19] each has reported autopsy-proved cases with a normal axis. In a review of the electrocardiographic patterns in 2,752 cases of congenital heart disease published by Neill and Brink[18] there were 81 cases of tricuspid atresia. Of these, 86.5 per cent showed left axis, 11 per cent normal axis, and only 2.5 per cent (2 cases) right axis deviation. Since the diagnosis was not established at autopsy, they were not included in our present review. In a series of 28 autopsy cases of tricuspid atresia,[19] the same authors found left axis deviation in 24 cases and normal axis in the remaining 4. To our knowledge the only proved case of tricuspid atresia with right axis deviation is an interesting one reported by Kjellberg[13] and associated with mirror-image dextrocardia.

Although overshadowed by the QRS axis deviation, the other electrocardiographic findings reported in cases of tricuspid atresia have received considerable attention. The P wave was frequently high and peaked in Lead II and in the right precordial leads. A high P wave and hepatic pulsations are said to suggest a relatively small interatrial communication. The unipolar limb leads pointed most often to horizontal position of the heart. The unipolar precordial leads usually revealed left ventricular preponderance.

When evaluating the electrocardiogram, the patient's age must be considered. During the first few months of life there is normally right axis deviation and right ventricular preponderance. In most normal infants the QRS axis gradually shifts toward the left and enters the normal range (30 to 90 degrees) at some time during the first 6 months. Right ventricular preponderance recedes during the first 6 months and gives way to left ventricular preponderance at about 1 year.[26] Left axis deviation with tricuspid atresia has been reported in an infant 2 days of age, and left ventricular preponderance reported at 4 weeks of age.

Numerous other cyanotic congenital conditions associated with left axis deviation have appeared in recent years. Included in these are Eisenmenger's complex, congenital mitral incompetence,[13] transposition of the great vessels,[28] cor triloculare biatriatum,[19] persistent truncus communis, Ebstein's anomaly, pentalogy of Fallot,[12] congenital methemoglobinemia, infantile coarctation,[29] left atrial drainage of the venae cavae, and double outlet right ventricle.[30] Thus, it is clear that the differential diagnosis of cyanosis due to congenital heart disease with left axis deviation includes a number of possibilities other than tricuspid atresia. Conversely, absence of deviation of the mean electrical axis to the left does not exclude the diagnosis.

SUMMARY

1. A review of the clinical and pathologic data concerning proved cases of tricuspid atresia has been presented.

2. Other cyanotic congenital conditions which may be associated with left axis deviation on the electrocardiogram are mentioned.

3. A case of tricuspid atresia (Type II-B) associated with right axis deviation has been described. We have been able to find only one other proved case of this anomaly with right axis deviation in a patient with dextrocardia.

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Unusual Postoperative Complications of Mitral Commissurotomy

Richard W. Watts, M.D., Cleveland, Ohio

The occurrence of emboli and the postcommissurotomy syndrome following mitral commissurotomy has been well documented. We wish to present three other, less commonly recognized complications of mitral commissurotomy: (1) left phrenic nerve palsy, (2) psychic changes, and (3) the postoperative appearance of murmurs from other valves. These complications have been observed in a series of 60 cases operated upon by Dr. Claude Beck in 1951 and 1952, and 29 cases operated upon by Dr. E. S. Rambousek from 1952 to 1957.

Left Phrenic Nerve Palsy.—The left phrenic nerve lies in a vulnerable position with respect to the necessary pericardiotomy for cardiac surgery. Since the nerve lies on the anterior surface of the pericardium, the usual pericardial incision parallels the nerve and is medial to it, with the phrenic nerve being displaced laterally. We have observed 3 cases with postoperative left diaphragmatic paralysis due to phrenic nerve injury. In the first case, persistent atelectasis of the lower lobe of the left lung with recurrent bronchopneumonia occurred until regeneration of the nerve obtained 3 months postoperatively. In the other 2 cases there has been only some reduction in vital capacity without complications, but there has been no evidence of nerve regeneration in 60 and 19 months, respectively. An additional case has also been noted after a Beck I coronary operation. It too has been free of complications although the vital capacity is reduced. Diaphragmatic function has not resumed in the 16 months since operation. Traction on the phrenic nerve presumably is the cause of the palsy, although the lack of resumption of function may indicate permanent damage in those cases. The use of fluoroscopy early in the postoperative period has helped in the detection of this condition, since diaphragmatic motion is better detected with fluoroscopy than by routine x-ray.

Psychic Changes.—The occurrence of psychic changes in the early postoperative period has been commented upon by several other observers.[1,2] In our series we observed a depressive reaction in 7 patients. All of these patients gradually recovered. During the recovery phase they had difficulty seeing well and complained of blurred vision, without scotoma or diplopia. An additional patient had an acute psychotic reaction characterized by auditory delusions. He recovered from the psychotic state spontaneously within 10 days, but had blurred

Received for publication Sept. 26, 1957.

vision for 3 months. Bailey[1] mentions that postoperative depression or psychosis occurred in 24 out of 811 patients. Two patients committed suicide. Three psychotic patients were successfully treated with electroconvulsive therapy in the early postoperative period. Bliss and associates[2] reported 4 schizophrenic reactions shortly after commissurotomy in 37 patients. One patient made a good recovery with the aid of electroconvulsive therapy. Another patient so treated developed apnea leading to death immediately after the third treatment. Two patients had brief schizophrenic reactions: in one characterized by delusions, in the other by auditory hallucinations without confusion or disorientation. Seven other patients showed psychic reactions, one of whom was confused for 3 days, while the others were anxious or depressed. Although the cause of these reactions is the subject of conjecture, most consideration has centered on the brief cerebral anoxia which is thought to be induced by obstruction of the mitral valve orifice by the surgeon's finger. Recent improvements in technique have apparently reduced the frequency of the occurrence of this complication. However, the occurrence of an acute schizophrenic reaction in other forms of heart surgery, such as in a 40-year-old man after the Beck I coronary operation, casts doubt upon the specificity of the previously mentioned etiology.

Murmurs From Other Valves.—Although apical systolic murmurs frequently appear after mitral commissurotomy, other and significant murmurs have also appeared in 2 patients. In one patient an aortic diastolic murmur appeared postoperatively; however, 64 months later there was no evidence of any hemodynamic significance. In the other patient systolic and diastolic murmurs presumably of aortic origin appeared after commissurotomy, but were without apparent hemodynamic significance 23 months later. Both patients had been examined before operation by several observers, none of whom had heard the aortic murmurs. It is presumed that the appearance of these murmurs is related to the increased cardiac output achieved following successful mitral commissurotomy. Uricchio and Likoff[3] have reported 2 cases in which aortic murmurs were audible before commissurotomy and in which successful operation was followed by left ventricular dilatation and failure, apparently due to the greater inflow into the left ventricle.

CONCLUSIONS

Three unusual complications of mitral commissurotomy are reported: (1) left phrenic nerve palsy, (2) psychic changes, and (3) postoperative appearance of murmurs from other valves.

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Familial Pulmonary Stenosis and Deaf-Mutism: Clinical and Genetic Considerations

Sanford M. Lewis, M.D., Benjamin P. Sonnenblick, Ph.D., Lawrence Gilbert, M.D., and David Biber, M.D., Newark, N. J.

The opportunity to observe multiple cases of congenital pulmonary stenosis in a single family constellation occurs infrequently. Detailed review of the literature discloses a description of this lesion in 2 sisters, reported in 1952,[1] and the subject is discussed generally in a comprehensive study recently published by Lamy and associates.[2] Except for these papers, however, and passing references in texts on congenital cardiac disease, there is almost no pertinent material available on the subject. The concomitant factor of deaf-mutism adds another element of intricacy and augments the possibility of genetic variations which warrant exploration.

The authors were prompted by these considerations to detail their observations of the Family W, in which the mother and 3 of 5 children exhibit clinical pulmonary stenosis, and 2 of these 3 children manifest coexisting deaf-mutism. Table I summarizes the significant facts about the family group as of the approximate time of clinical study (1956-57).

Significant clinical features of the 4 cases of pulmonary stenosis are recorded in the Case Reports.

TABLE I

NAME	AGE (YEARS)	PULMONARY STENOSIS	DEAF-MUTISM
Mr. W.	77	No	No
Mrs. W.	36	Yes	No
Ann	12	No	No
Harry	11	Yes	Yes
Brenda	6	Yes	Yes
David	4	No	No
Mary	2	Yes	No

From the Cardiodynamics Department, Beth Israel Hospital, Newark, N. J., and Rutgers University, Newark, N. J.

Received for publication Sept. 27, 1957.

CASE REPORTS

CASE 1.—Mrs. W. The patient is a 36-year-old Negro woman, gravida 5, para 5. The family history, including her parents, brother, and 3 nieces, is negative for congenital or cardiac disease. There is no past history of viral or other infectious disease during any of the 5 gestations. The patient recalls slight dyspnea on exertion since childhood, but there is no other pertinent symptomatology.

Cardiac examination suggested no enlargement. The aortic and pulmonic sounds were equal and of good intensity. A harsh Grade 3 systolic murmur was heard loudest at the pulmonic area, with radiation toward the apex. Rhythm was regular; sinus and brachial blood pressure was 118/80 mm. Hg. There were no other significant physical findings.

The electrocardiogram revealed a vertical heart. No abnormalities were noted. A teleoroentgenogram of the chest indicated cardiac contours well within normal limits of size and configuration. The lung fields manifested a slight accentuation of the vascular markings in both hilar areas. Angiocardiographic studies revealed no shunt. Findings characteristic of post-stenotic dilatation of the pulmonary artery were observed.

Catheterization of the right heart revealed the following blood oxygen concentrations: superior vena cava—13.8 per cent; inferior vena cava—9.5 per cent; proximal right atrium—14.0 per cent; inflow tract right ventricle—12.8 per cent; mid-right ventricle—13.4 per cent; pulmonary artery—13.2 per cent; femoral artery—17.0 per cent. The femoral artery blood was 95 per cent saturated. Right ventricular pressure was 38/3 mm. Hg, and pulmonary artery pressure was 15/5 mm. Hg, with a mean pressure of 10 mm. Hg. The findings were compatible with pulmonary stenosis. There was no evidence of shunt.

Because of the patient's excellent clinical condition, the absence of evidences of deterioration from a cardiovascular viewpoint, and the limited elevation of right ventricular pressure, it is felt that corrective surgery is not required at present.

CASE 2.—Harry. The patient is an 11-year-old Negro boy. A cardiac murmur was known to the mother since birth, and the child exhibited dyspnea on effort from his earliest days. No other cardiac stigmata were noted. Development was considered normal except for congenital deaf-mutism.

Examination of the heart revealed no enlargement. The pulmonic second sound was absent. A Grade 4 rough systolic murmur was heard throughout the anterior and posterior chest, loudest in intensity at the second intercostal space near the left sternal border. A systolic thrill was palpable at this point. Rhythm was regular sinus, and brachial blood pressure was 120/64 mm. Hg. There were no other physical findings of importance.

The electrocardiogram indicated a vertical heart. Prominent R waves of high amplitude in Leads aV_R and V_1 were compatible with a diagnosis of right ventricular hypertrophy. X-ray examination of the chest revealed normal pulmonary markings. Angiocardiograms indicated a moderate degree of stenosis of the infundibulum of the right ventricle, with dilatation of the main pulmonary artery distal to the stenotic area.

Catheterization of the right heart revealed the following blood oxygen concentrations: superior vena cava—12.0 per cent; inferior vena cava—12.0 per cent; mid-right atrium—12.1 per cent; mid-right ventricle—12.2 per cent; outflow right ventricle—11.9 per cent; pulmonary artery—12.2 per cent. The femoral artery blood was 95 per cent saturated. Pressure in the right ventricle was 115/0 mm. Hg, and in the pulmonary artery 12/6 mm. Hg. The findings were compatible with a fairly high degree of pulmonary stenosis. No shunt was demonstrated.

The large right ventricular-pulmonary artery gradient and the evidence of right ventricular hypertrophy are considered to be indications for surgical correction of the stenosis. The child, however, is presently in a state institution because of his deaf-mutism, and surgery has not yet been performed.

CASE 3.—Brenda. The patient is a 6-year-old Negro girl who has exhibited deaf-mutism since birth. During treatment for an episode of bronchitis, at the age of 5 years, a murmur was first described. There have been no complaints of dyspnea, cyanosis, or other pertinent symptoms.

On examination there was no cardiac enlargement. The pulmonic second sound was markedly diminished. A harsh Grade 3 systolic murmur was heard loudest at the pulmonic area

with transmission throughout the anterior and posterior chest. A systolic thrill was appreciated over the pulmonic area. Rhythm was regular sinus; brachial blood pressure was 130/78 mm. Hg.

The electrocardiogram indicated a vertical heart with considerable clockwise rotation. QS deflections in Leads I and aV_L, and tall R waves in Leads aV_R and V_1 were consistent with right ventricular hypertrophy. A teleoroentgenogram of the chest revealed normal pulmonary markings. The cardiac silhouette was within normal limits of size and configuration.

Catheterization of the right heart revealed the following blood oxygen concentrations: superior vena cava—12.0 per cent; inferior vena cava—12.6 per cent; proximal right atrium—12.4 per cent; distal right atrium—12.6 per cent; right ventricle—12.9 per cent; pulmonary artery—12.5 per cent. Pressure in the right ventricle was 60/0 mm. Hg, and in the pulmonary artery was 24/12 mm. Hg. As the catheter was pulled through the pulmonary artery toward the right ventricle, several intermediate pressure pulses were noted, suggesting that the stenosis was of the infundibular type.

Because of the patient's youth, the complete absence of symptomatology, and the lack of markedly high right ventricular pressures, surgery has been deferred for the present.

CASE 4.—Mary. The patient is a 2-year-old Negro girl who has developed normally and exhibits no dyspnea or cyanosis. A murmur has been present since birth.

Examination of the heart did not suggest enlargement. The pulmonic second sound was almost inaudible. A harsh Grade 4 systolic murmur was heard throughout the chest, with accentuation at the pulmonic area, where a systolic thrill was palpable. Rhythm was regular sinus.

The electrocardiogram indicated a vertical heart. Deep S waves were observed in Leads I, II, III, and aV_F. There was a tall late R wave in aV_R and V_1, and there were RS deflections across the chest through V_6. These findings were suggestive of right ventricular hypertrophy. A teleoroentgenogram indicated normal pulmonary markings. The cardiac contours were somewhat suggestive of right ventricular enlargement.

Because of the child's age and an absence of clinical urgency, catheterization has not been performed. It is felt, nevertheless, that a diagnosis of pulmonary stenosis is tenable. Further observation is planned.

DISCUSSION

Conventional examination of the 4 patients cited, supplemented for the most part by angiocardiographic and catheterization studies, justifies a diagnosis of pulmonary artery stenosis in each instance. Except in the case of Harry, right ventricular pressure has not suggested high grades of obstruction, and there have been, fortunately, no episodes of frank decompensation or other complications. None of the patients presents evidence indicating the possibility of acquired cardiac disease, and no unusual electrocardiographic findings have been observed. A recent report by Jervell and Lange-Nielsen[3] describes concomitant congenital deaf-mutism and functional heart disease with prolongation of the Q-T intervals. This deviation has not been noted in our studies. Deaf-mutism, in each of the cases cited, was observed virtually from birth, and there is consequently little doubt as to the validity of its congenital classification.

Table I indicates the members of the W family under direct consideration, and gives their respective ages at the time of the study. It must be emphasized that the only individuals examined were the mother and those children with relevant cardiac and sensory-motor anomalies. The husband and 2 other children were not available for examination. Mrs. W., however, is cooperative and intelligent, and has been able to supply considerable information concerning these individuals as well as her only other relatives, namely, her parents, her brother and his female children.

Of negative significance etiologically are the facts that Mr. and Mrs. W. are not related, are the parents of all 5 children, and present a family history devoid of congenital stigmata. The sharp age disparity between husband and wife is noteworthy. There is no history during any of the 5 pregnancies of rubella or other viral infections, and obstetrical complications did not occur.

Little information concerning the role of heredity as a contributing factor in the etiology of congenital pulmonary stenosis per se is available in the literature or representative texts on human genetics,[4-7] other than an occasional reference to this lesion as one of the malformations comprising the tetralogy of Fallot.[8] Consequently, a decided paucity of data exists concerning the influence of any specific gene or genes in the development of pulmonary stenosis, or the type of heredity mechanism involved. From the medical point of view there is also a minimum of information relative to the etiologic significance in pulmonary stenosis of extrinsic factors such as nutritional deficiencies during pregnancy, maternal skeletal anomalies, syphilis and fetal endocarditis, viral infections in early pregnancy, and racial or geographic variants.[9]

On the basis of data concerning the Family W, obtained either directly or communicated to us, and because of the essential similarity of the several cases of pulmonary stenosis, we may postulate that this familial concentration of anomalies does have an hereditary etiology and that at least two major genes are operative. One, a dominant gene which could be either autosomal or sex-linked, may have played a determinative role in the manifestation of the cardiac defect evident in the mother, in 1 of her 2 sons, and in 2 of her 3 daughters. A second gene, recessive and autosomal, may be assumed to have been carried by both parents. According to this interpretation, 2 of the 5 children are homozygous for the recessive genetic factor, having received it from both parents, with the resultant manifestation of deaf-mutism. These postulates represent a simple and necessarily provisional consideration of the role of hereditary factors in the causation of the anomalies described. Evaluation of other potential facets of the problem such as the role of modifying genes, of gene-environmental interactions, of penetrance and of expressivity of the traits in question must await the accumulation of much additional information.

Lamy and co-workers,[2] in addition to surveying the pertinent literature, analyze their own series of 1,118 cases, which include 56 examples of pulmonary valvular stenosis. No pedigrees are presented. They conclude that both genetic and nongenetic factors are operative in the etiology of congenital heart disease and that the relative importance of each varies substantially from one clinical subgroup to another. Of immediate interest is their finding that genetic factors are especially important in the development of pulmonary stenosis as compared with other congenital cardiac lesions. The view that pulmonic stenosis may have a larger genetic component than other major congenital cardiac defects is sustained by noting the particularly high incidence of consanguinity of parents whose children exhibit this anomaly (as compared with controls), as well as the high incidence of such lesions among the sibs.

Parental age, as reported by Lamy and co-workers, appears to be of little or no etiologic significance, averaging about the same in the case and control

groups. The male parent in Family W was approximately 62 years of age at the conception of his first child, and he subsequently fathered 4 other sibs. With respect to the cardiac lesion, it is the mother who is affected and therefore represents the individual most likely responsible for transmitting the postulated hereditary factor significant for the development of pulmonary stenosis. The sensory-motor abnormality, as stated above, may become manifest in the progeny who are homozygous for an autosomal recessive gene borne by both carrier parents.

SUMMARY

1. A unique family group is described in which the mother and 3 children exhibit clinical pulmonary stenosis, and 2 of the 3 children manifest concomitant deaf-mutism.

2. The possible role of extrinsic etiologic factors is discussed, and their apparent absence emphasized.

3. A genetic mechanism is postulated in which a dominant gene contributed by the mother is determinative for the cardiac lesion, and a recessive gene transmitted by both parents is important for the manifestation in homozygous offspring of the sensory-motor abnormality.

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Unruptured Congenital Aortic Sinus Aneurysm With Aneurysmal Dilatation of the Aorta and Aortic Regurgitation Without Arachnodactyly

T. K. Lin, M.D., A. M. Diehl, M.D., J. W. Walker, M.D., T. N. Hall, M.D., and D. C. Peete, M.D., Kansas City, Kans.

The unusual association of unruptured congenital aortic sinus aneurysm, congenital aneurysmal dilatation of the aorta, and aortic regurgitation without accompanying arachnodactyly or aortic coarctation has not been reported previously. Extensive cardiovascular studies have been carried out in this case since this is the youngest patient in whom the ante-mortem diagnosis of unperforated aortic sinus aneurysm has been made.

CASE REPORT

N. L. R. was born April 16, 1949, by breech delivery of a normal pregnancy. The prenatal history was uneventful. He was thought to be well until 1 year of age, at which time he began having episodes of lethargy, precordial overactivity, and moderate dyspnea lasting about 24 hours. The parents were informed that the child had heart disease. However, admission to the Children's Mercy Hospital was not accomplished until March, 1952, when he was nearly 3 years of age. Angiocardiographic studies were performed on March 12, 1952. Six serial films were made with 2-second intervals after the injection of 20 c.c. of 70 per cent Diodrast. There was distinct filling of a markedly dilated ascending aorta and right aortic sinus (sinus of Valsalva) 6 seconds after the dye filled the right atrium (Fig. 1). The child was referred to the University of Kansas Medical Center 2 months later because of more frequent occurrence of these attacks, fever, and tachypnea. Physical examination revealed a slightly underdeveloped and fairly well-nourished boy who was febrile (102°F.), lethargic, and appeared acutely ill. Blood pressure was 80/20/0 mm. Hg in both arms. The femoral pulses were of the Corrigan type without systolic delay. Pistol-shot sounds and Duroziez' signs were present over the femoral arteries. The throat was congested. There was bulging of the precordium. Scattered, coarse, moist râles were detected over the left chest posteriorly. The second sounds over the aortic and pulmonary areas were of normal intensity. There were Grade 6 systolic and diastolic murmurs over the aortic area, with corresponding Grade 2 thrills. The diastolic murmur was best heard along the left sternal border.

The electrocardiogram showed left ventricular hypertrophy (Fig. 2). Fluoroscopy of the heart disclosed marked enlargement of the left ventricle. The main pulmonary artery segment, the right ventricle, and the right pulmonary artery were normal. There was marked dilatation of the ascending aorta with vigorous pulsation. The left ventricular pulsation was also extremely active. The barium swallow demonstrated the aortic arch to be on the left. Laboratory tests were normal. The serology was negative.

From the Departments of Internal Medicine and Pediatrics, University of Kansas Medical Center, Kansas City, Kans., and The Children's Mercy Hospital, Kansas City, Mo.

Received for publication Oct. 9, 1957.

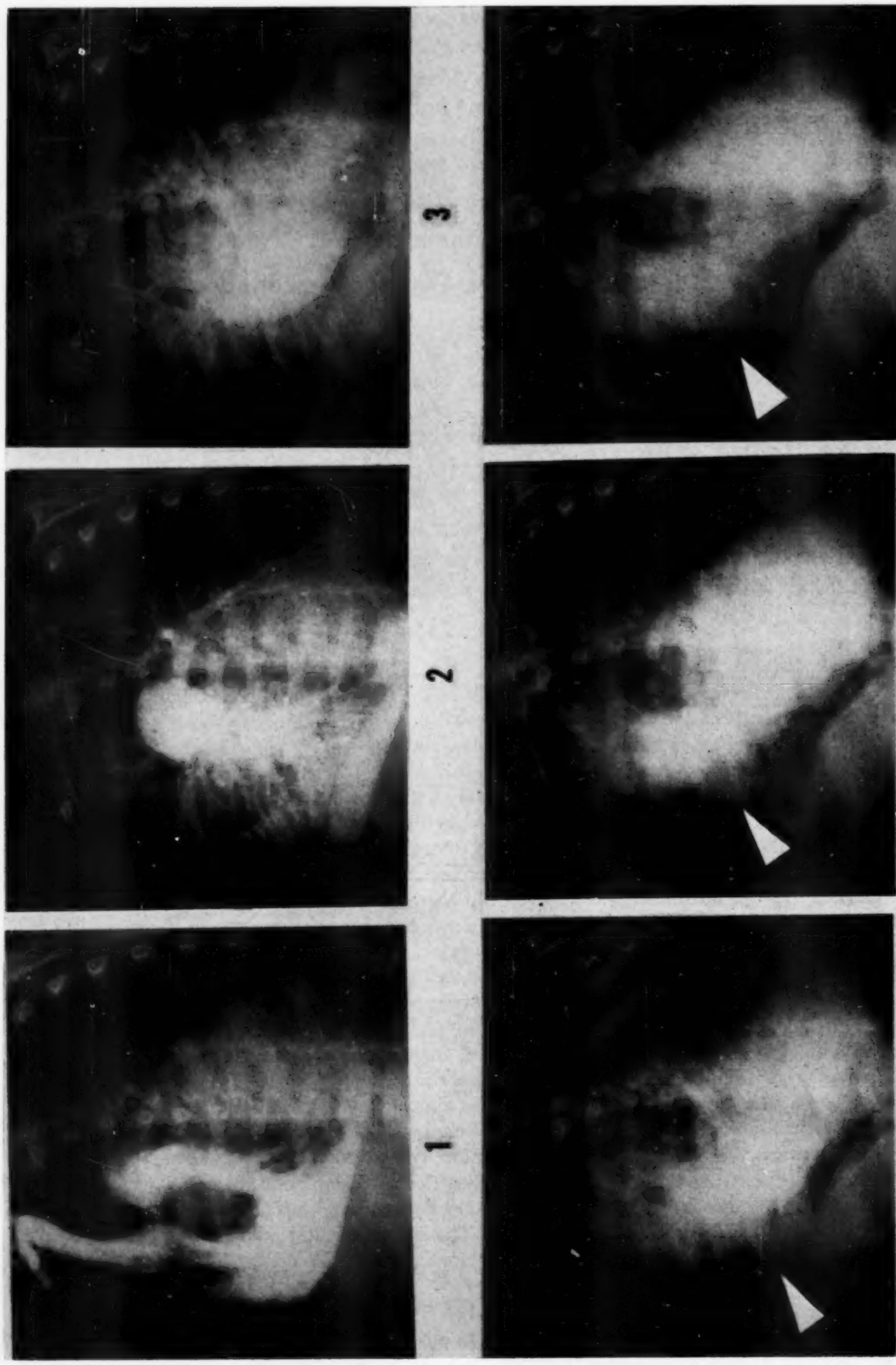

Fig. 1.—Angiocardiogram showing aneurysmal dilatation of the aorta and marked enlargement of the left ventricle. The arrow indicates the aneurysm of the right coronary sinus.

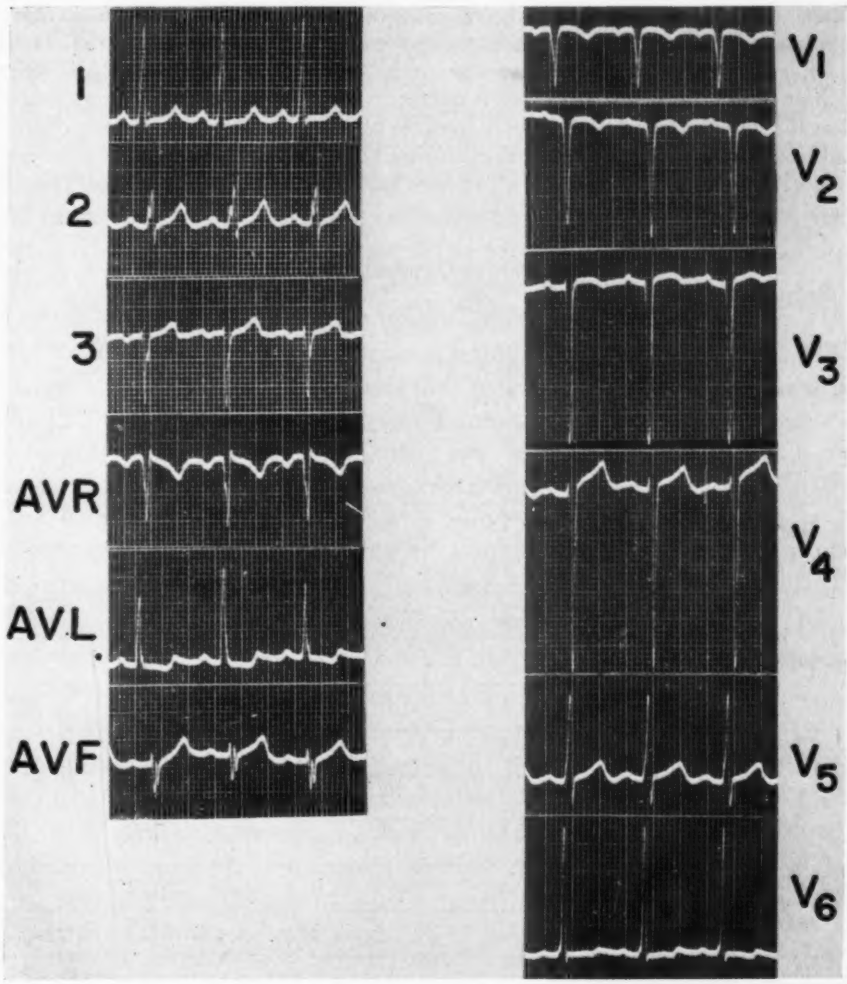

Fig. 2.—Electrocardiogram showing marked left ventricular hypertrophy and myocardial ischemia.

Fig. 3.—Phonocardiogram showing crescendo-decrescendo systolic and diastolic murmurs. Logarithmic speed 75 mm./sec. Aortic area.

Fig. 1.—Angiocardiogram showing aneurysmal dilatation of the aorta and marked enlargement of the left ventricle. The arrow indicates the aneurysm of the right coronary sinus.

The infectious process causing the fever responded to parenteral penicillin therapy. However, the boy was subsequently hospitalized twice for bronchopneumonia and possible associated left heart failure. Cardiac catheterization was carried out Dec. 5, 1955 (Table I). The pressures in the chambers of the right heart were normal. An anomalous pulmonary vein draining into the left innominate vein was suspected because of the unusually high oxygen content in the left innominate vein. The arterial pressure tracing obtained from the femoral artery showed a marked increase of the pulse pressure (150/35 mm. Hg). A phonocardiogram confirmed the presence of both aortic systolic and diastolic murmurs (Fig. 3).

TABLE I. CARDIAC CATHETERIZATION STUDY

SOURCE OF BLOOD SAMPLE		OXYGEN CONTENT* (VOL. %)	OXYGEN SATURATION* (%)	PRESSURE (MM. Hg)	
				S/D	MEAN
Left subclavian vein		13.38	71.5		
Left innominate vein		16.73	89.2		
Superior vena cava		13.14	69.8		7
Right auricle	close to SVC	13.71	73.1		
	mid	13.38	71.5		2.5
	close to IVC	11.13	59.1		
Right ventricle	inflow	11.56	61.0		
	mid	11.25	60.2	25/0	11
	outflow	11.99	63.9		
Pulmonary artery	main	11.80	63.0	25/12	18
	right	11.51	61.2	25/12	18
Pulmonary artery wedge					10
Femoral artery		18.16	96.7	150/35	78

*Oxygen capacity: 19.12

Since 1955, he has been re-evaluated at 4-month intervals as an outpatient. His clinical symptomatology and physical findings remain unchanged. Digitalization for left heart failure has not been necessary thus far.

DISCUSSION

Aneurysms of the aortic sinuses are rare. Somewhat over thirty-five cases of congenital aortic sinus aneurysms have been reported.[1-4] Ten cases of unperforated aortic sinus aneurysms have been described in the medical literature, one of which was symptomatic,[3] three had an associated coarctation of the aorta,[5] one had a coarctation of the aorta and subacute bacterial endocarditis,[6] one had a pseudo-coarctation,[7] three had arachnodactyly,[8] and one had both congenital aortic and mitral stenosis.[9] Two of the ten cases had diastolic murmurs of aortic regurgitation.[6,8]

Since Erdheim's classic description of cystic medial necrosis,[10] there have been several reports regarding dissecting aortic aneurysms, aneurysmal dilatation of the aorta, ectopic lenses, arachnodactyly, and Marfan's syndrome.[11-17] However, the unusual association of an unruptured congenital aortic sinus aneurysm and congenital aneurysmal dilatation of the aorta with aortic regurgitation, but without arachnodactyly or aortic coarctation, has not been reported.

The embryologic explanation of these defects is probably based upon a combination of the failure of fusion between the proximal and distal bulbar swellings, and a developmental defect of the elastic tissue at the base of the aorta.[1-4,10,15-17] Symptoms of an unruptured aortic sinus, if present, are not specific. However, the physical findings caused by associated lesions such as aortic coarctation, aortic regurgitation, or Marfan's syndrome are usually outstanding and frequently pathognomonic. The electrocardiographic changes follow closely the degree of systolic and diastolic overloading caused by these associated anomalies. In the absence of systemic hypertension, syphilitic aortitis, atherosclerosis, patent ductus arteriosus, and aortic coarctation the unusual vigorous pulsation at the root of the aorta, demonstrated by conventional cardiac fluoroscopy, frequently indicates the presence of congenital aneurysmal dilatation of the aorta. Angiocardiography or retrograde selective aortography will usually verify the presence of an unperforated aortic sinus aneurysm as well as the diffuse dilatation of the aorta.

Surgical attempts to repair a ruptured aortic sinus aneurysm were not successful until the recent application of the pump-oxygenator.[18-20] The presence of aneurysmal dilatation of the aorta adds further to the difficulty in the surgical management of this lesion. Correction of the aortic sinus aneurysm when unruptured, as in this case, is not justified without the simultaneous alleviation of the severe aortic regurgitation caused by the aneurysmal dilatation of the aorta. However, the remote possibility of the aortic sinus aneurysm rupturing into the left ventricle cannot be excluded.

SUMMARY

1. An unusual case of unruptured congenital aortic sinus aneurysm with aneurysmal dilatation of the aorta and aortic regurgitation without arachnodactyly is reported.

2. Cardiac catheterization and angiocardiographic studies are presented and discussed.

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Reciprocal Beating of the Atria

Frederic L. Eldridge, M.D., San Francisco, Calif.*

In 1915, White[1] reported a patient whose electrocardiogram showed an A-V nodal rhythm with occasional ventricular bigeminy in which there was a P wave sandwiched between the paired QRS complexes. He proposed that this represented alternate stimulation of the atria and ventricles. Drury,[2] reporting a similar case in 1924, recognized that this clinical condition had some similarity to the reciprocating rhythm of Mines[3] in which alternate beating of the auricle and ventricle, the one seeming to stimulate the other, followed electrical stimulation of the heart of the frog or electric ray. Drury termed the nonrepetitive clinical condition "reciprocal rhythm." Dock,[4] in 1928, separated this isolated type of alternate beating (reciprocal) from the continuous variety described by Mines (reciprocating) because no examples of the latter had been produced experimentally or noted clinically in the mammalian heart. Since that time, however, reciprocating rhythm has been produced in the dog's heart[5,6] and several possible examples have been noted in human beings.[7-13] Most authors are agreed that the mechanisms of both types are similar, so that the distinction is useful mainly in description.

Examples of reciprocal rhythm have not been reported frequently, and ones of the reciprocating variety even less so. Zakopoulos,[13] in 1957, recorded a total of only 38, five of which were of the repetitive type. Scherf and Schott,[14] in a critical review in 1953, rejected some of the reported reciprocal rhythms and most of the reciprocating ones as having other possible explanations. Nevertheless, it is a condition which is probably very often overlooked, misdiagnosed, or not reported. Katz and Pick,[15] for example, mention having found 40 examples of reciprocal rhythm in their series of about 100,000 records in 50,000 consecutive patients.

Most cases in the literature are associated with A-V nodal rhythm in which a retrograde stimulus from the node to the atrium turns around and restimulates the ventricle, thereby causing the QRS-P-QRS "sandwich" described by White,[1] and there have been reports of a similar reciprocal mechanism following retrograde conduction of idioventricular or extrasystolic beats.[14,16-18]

From the Department of Medicine of the Stanford University School of Medicine, San Francisco, Calif.

Received for publication Oct. 1, 1957.

*Scholar in Medical Science of the John and Mary Markle Foundation.

Under certain conditions it should be possible for reciprocal beats to occur as well in sinus rhythm. Here the stimulus would go to the A-V node, thence to both the ventricle and atrium. This would produce a P-QRS-P "sandwich." Since the second P wave would result from atrial activation in retrograde fashion, it should have a different configuration from the first. Katz and Pick[15] have suggested the terms "reciprocal beating of the atria" or "reversed reciprocal beating" for this mechanism.

Only a very few possible examples of reciprocal beating of the atria have been reported.[9-11,13,15,19,20] The present report is that of a patient who exhibited markedly prolonged A-V conduction time, 2:1 A-V heart block, and probable reciprocal beating of the atria.

CASE REPORT

The patient was a 48-year-old man who gave a definite history of rheumatic fever, with swollen joints at the age of 15 years. A heart murmur had been noted repeatedly since then. One year prior to being seen in this hospital, syncope had developed when he stood or exercised. Heart block had been noted at that time, and he was treated with thyroid and ephedrine with some benefit. When seen he complained of tiring easily and of his heart "skipping beats."

He was a husky man who looked well. His heart was regular at 32 beats per minute. Blood pressure was 180/65 mm. Hg. Musical râles were present. His heart did not seem enlarged and the apical impulse was normal but slow. An early systolic ejection murmur was heard over most of the precordium but was loudest in the aortic area and was transmitted to the neck vessels. Two atrial waves were noted in the jugular pulse, one preceding and one occurring just after the onset of the carotid pulse. The remainder of the physical examination was negative.

A standard 12-lead electrocardiogram (Fig. 1) showed the pattern of complete right bundle branch block and a ventricular rate of 33 per minute with the rhythm described below. Vibrations of an early systolic murmur at the aortic area were seen in the phonocardiogram (Fig. 2). A superimposed carotid and jugular pulse tracing (Fig. 2) revealed a large atrial wave, its peak occurring 0.16 sec. after the onset of the sinus P wave, and a second atrial wave superimposed upon the carotid pulse, its peak also occurring 0.16 sec. after the second P wave.

Cardiac Rhythm.—The rhythm present most of the time, a sinus mechanism with a prolonged P-R interval (0.44 sec.), is shown in the top strip of Fig. 3. The axis of the sinus P wave is normal (+45°). Following each QRS complex by 0.23 sec. is a second P wave (P′) which has a markedly different axis (−75°) than the sinus P wave. In Leads II and III (Fig. 1) this P′ wave is inverted. The P-P′ interval is 0.67 sec. Exercise caused a change in ventricular rate (from 32 to 38 per minute) but had no effect upon the P-R interval or upon the relationships of the P-QRS-P "sandwiches" (Fig. 4).

The bottom two strips of electrocardiographic record in Fig. 3 were obtained during the performance of a Valsalva maneuver. In two cycles, at which time the ventricular rate is not significantly altered, the premature inverted P wave does not occur. This change allows the 2:1 A-V block rhythm to become apparent.

On one occasion, a strip of record was obtained (Fig. 5) which shows the usual P-QRS-P set of complexes but with a different R-P′ interval, longer (0.34 sec.) than the usual 0.23 sec. The P-P′ interval in this portion of record is 0.76 sec. There is no change in the configuration of the second P wave during this period.

DISCUSSION

The constancy of the prolonged P-R interval in this case during changing heart rate leaves no doubt that the sinus P waves are conducted to the ventricle. It is also apparent that the normal but nonconducted sinus P waves of the 2:1

A-V heart block rhythm are blocked by the premature atrial activity that occurs throughout most of the electrocardiographic record. The activity of the sinus node, as diagrammed in Fig. 3, is not interfered with, indicating the presence of a protective perifocal block around this structure. The problem raised in this case is that of trying to decide upon the mechanism leading to these premature inverted P waves. The four possible causes are: (1) atrial parasystole, (2) automatic or (3) coupled atrial premature systoles, and (4) reciprocal beating of the atria.

Atrial parasystole can easily be ruled out by the constant time relationships, throughout all of the record, of sinus P waves and QRS complexes and the premature P waves. Automatic atrial premature systoles triggered by the mechanical contraction of the ventricle would not explain the shift in the QRS-P′ interval seen in Fig. 5.

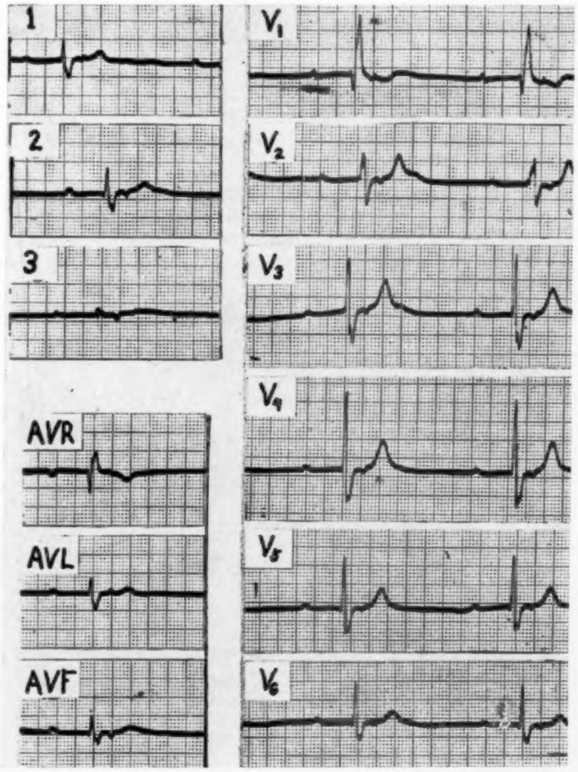

Fig. 1.—Twelve-lead electrocardiogram showing right bundle branch block pattern.

The distinction between coupled atrial premature systoles and reciprocal beating of the atria is not so easy to make. The abnormal axis and inversion of the premature P waves in Leads II and III result from retrograde activation of the atria. Although this has been used by some authors as evidence of nodal activation and reciprocal rhythm, it unfortunately does not help in the distinction because retrograde activation of the atria can occur from a low atrial focus as well.

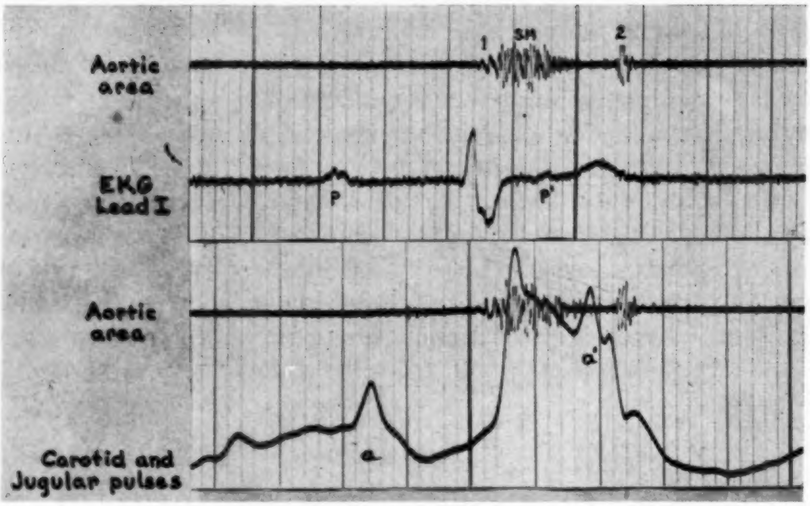

Fig. 2.—All 4 tracings are superimposed in time. The aortic area sound tracing shows an early systolic murmur. The lower tracing represents superimposed carotid and jugular pulse waves and shows, in addition to the arterial pulse, an atrial wave (a) 0.16 sec. after the sinus P wave (P), and a second atrial wave (a') 0.16 sec. after the premature P wave (P'). Time intervals are 0.04 sec.

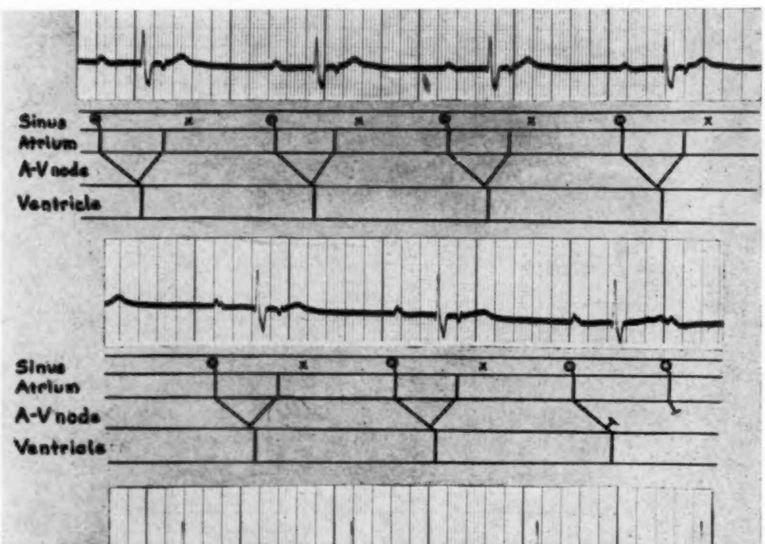

Fig. 3.—Timing lines represent an interval of 0.04 sec. Top strip: Electrocardiogram (Lead II) taken at rest, showing mechanism of reciprocal beating of the atria. The symbol x indicates the probable position of blocked sinus impulses. Middle and lower strips: Electrocardiogram (Lead II) showing the appearance of ordinary 2:1 A-V block during the Valsalva maneuver.

The blocking of the premature P waves by vagal stimulation also does not help in differentiating between the two causes, for, while experimental studies[5] have shown that vagal stimulation can produce a retrograde conduction block between A-V node and atria, it also may have the effect of stopping atrial premature systoles.

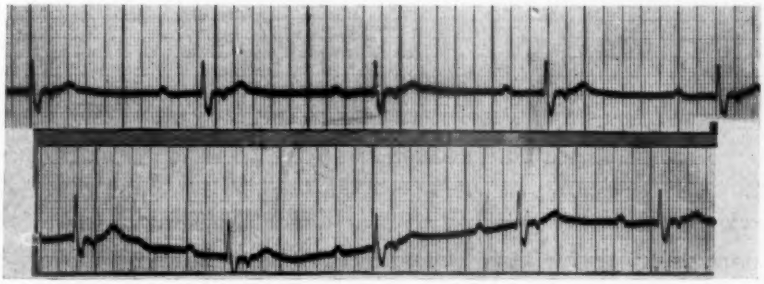

Fig. 4.—Electrocardiogram (Lead II) showing increase of ventricular rate (from 32 to 38 per minute) following mild exercise. There are no changes in P-R, R-P′, or P-P′ intervals. The top strip was taken during rest, the bottom strip following exercise. Time intervals are 0.04 sec.

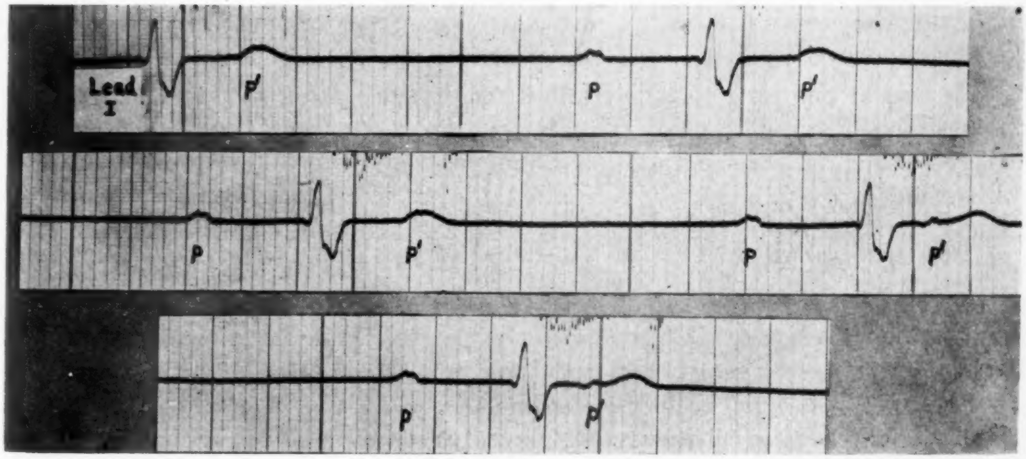

Fig. 5.—Continuous strip of electrocardiogram (Lead I) showing a spontaneous change of R-P′ and P-P′ intervals. Time intervals are 0.04 sec.

If coupled atrial premature systoles were the cause of this rhythm, they would be due to re-entry in the lower part of the atrium with retrograde activation of the atria. However, the P-P′ interval throughout most of the record is 0.67 sec. This is outside the usual limits for coupled premature systoles.[14] Furthermore, as shown in Fig. 5, the P-P′ interval changed on one occasion and was, for several beats, longer (0.76 sec.) than the usual 0.67 sec. In the case of atrial premature systoles this would mean a changing of the coupling and an even longer coupling time.

A more likely explanation would seem to be that all of the premature P waves are due to retrograde conduction from the A-V node, that this retrograde

conduction can vary or be blocked, and that the mechanism is one of sinus beats with reciprocal beating of the atria. Admittedly, such a mechanism is not proved, but it must be remembered that the only really basic difference between coupled atrial premature systoles and reciprocal beating of the atria is that of the location of the re-entry mechanism, the former being in the atrium and the latter in the A-V node. In view of the precarious state of nodal conduction here, a condition known to predispose to reciprocal rhythm, it seems reasonable to assume that in this case the re-entry locus is in the A-V node.

The difference in the P-R and R-P′ conduction times exhibited here is of little significance since the QRS complex represents an arbitrary point of measurement. Since there is no way of determining when or where retrograde conduction actually starts in the node, it is impossible to say anything about the rate of retrograde conduction as compared to that of forward conduction.

Various types of reciprocal rhythm have been reviewed by Bix.[11] It is clear that both A-V nodal rhythm and ventricular rhythms can give rise to reciprocal beats, but Scherf and Schott[14] reject most of the cases reported as reciprocal beating of the atria, believing that they can be explained more readily by some other mechanism, such as atrial premature systoles or paroxysmal atrial tachycardia. Recently, however, Moe and his co-workers[6] have shown experimentally in the dog that reciprocal beating of the atria can occur after sinus beats, a finding which supports the possibility of its occurrence in human beings.

It was at one time considered that reciprocal beating might be due merely to mechanical stimulation of the adjacent heart chamber, but the finding of delayed and variable retrograde conduction is strongly against this interpretation. All authors now agree that the reciprocal rhythm is due to a re-entry mechanism, usually at the level of the A-V node. Pick and Langendorf,[21] for example, consider the delayed retrograde conduction in cases of reciprocal beating to be convincing evidence of a re-entry mechanism in the human heart.

Various mechanisms of conduction in the A-V node have been proposed to explain the different types of reciprocal rhythm. Most cases have been explained on the basis of a functional longitudinal dissociation of the upper A-V nodal tissue,[5] in which some fibers are left undischarged by the initial activation wave. Tenney[22] has proposed a similar mechanism to explain reciprocating rhythm found in the lepidopteran heart. Danielopolu and Proca[23] postulated a functional intra-atrial block, and Decherd and Ruskin[24] and Zakopoulos[13] an area of refractory nodal tissue of varying size and shape, to explain their cases of reciprocal rhythm with double atrial stimulation.

Recently, Moe and his associates[6] have, as a result of their experimental work in the dog, postulated that the A-V transmission system is normally composed of two pathways, one having a shorter refractory period but a longer conduction interval than the other. They propose that reciprocal rhythm will occur whenever the basic frequency of impulses is too rapid to allow recovery of the usual fast pathway. When this happens the slower pathway will conduct the impulse, leaving the faster pathway available for the return passage. Although this mechanism amounts to a functional longitudinal dissociation of nodal

tissue, since two separate pathways are used, the concept is different in that both pathways are considered normal. In both mechanisms the re-entry occurs in the A-V node.

The dual A-V conduction system hypothesis would appear to be a suitable explanation for the present case. The fact that the basic frequency of atrial impulses is not rapid (64 per minute) does not rule out this mechanism, for it is not a question of absolute impulse frequency but of a frequency too rapid for a given conduction system. The prolonged A-V conduction and 2:1 A-V heart block show that the latter condition is fulfilled in this case in spite of the slow atrial rate.

It seems probable that the dual A-V conduction system hypothesis provides a single explanation for most of the reported cases of reciprocal rhythm, including those with double atrial stimulation.[13,24]

SUMMARY

A probable case of reciprocal beating of the atria in a patient with prolonged A-V conduction and 2:1 A-V heart block is reported. The difficulties in making this diagnosis are discussed.

The author is grateful to Dr. Arthur L. Bloomfield for the opportunity to study and report this patient, and to Dr. David A. Rytand for helpful advice.

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The Hypocholesterolemic Effect of Nicotinic Acid, Phenyl-Ethyl-Acetic Acid Amide, and a Combination of Both, in Dogs. Preliminary Communication

Francisco Comesaña, M.D., Armando Nava, M.D., Bernardo L. Fishleder, M.D., and Demetrio Sodi-Pallares, M.D., Mexico, D. F.

There is an increasing interest in finding pharmacons capable of removing cholesterol, for the purpose of treating those ailments in which hypercholesterolemia is present. For some time now (since 1955), one of us (D.S.-P.) has observed a reduction in the cholesterol levels in the blood of patients treated with nicotinic acid. Nevertheless, prior to these observations, Altschul and associates[1,2] published two reports of their work in which they studied the influence of nicotinic acid on the cholesterol serum in rabbits and in human beings. The authors demonstrated that nicotinic acid decreases the cholesterol serum just as much in normal individuals as in those who have hypercholesterolemia, and that in the latter the cholesterol decrease was more important than in the former. On the other hand, the amide of the nicotinic acid did not show a definite influence on the cholesterol of 29 healthy students. Encouraged by these findings, we tried a series of experiments in order to verify the usefulness of nicotinic acid in decreasing the cholesterol content, as well as to clarify its pharmacodynamics.

Having in mind the action of phenyl-ethyl-acetic acid amide on the cholesterol present in blood,[3,4] we studied the association or combination of nicotinic acid with phenyl-ethyl-acetic acid amide in order to increase the hypocholesterolemic action. Both the nicotinic acid as well as the phenyl-ethyl-acetic acid amide lower the cholesterol in the blood; but, as we shall see in this communication, the action is quicker and more noticeable when the two pharmacons are combined.

METHOD OF STUDY

The experiments were conducted on eleven normal dogs with weights varying between 18 and 21 Kg. In order to avoid cumulative effects we allowed a few days' rest in between the administration of the drugs, whether administered alone or in combination. The oral administration was given from Monday to Friday, suspending the administration of the drugs on Saturday and Sunday. The animals were divided into 3 groups: each group of animals received each of the drugs and a combination of both drugs, but in a differing order, for a period of 5 days with intermediate rests of 9 days. In the beginning, the first group received 50 mg. of nicotinic acid. Later, a dose of 400 mg. of phenyl-ethyl-acetic acid amide was given. Still later the combination of 50 mg. of nicotinic acid and 400 mg. of phenyl-ethyl-acetic acid amide was administered. The second group received the drugs in the following order: phenyl-ethyl-acetic acid amide, nicotinic acid, and the combined drugs. The third group was given theirs in the following order: the combined drugs, the nicotinic acid, and the phenyl-ethyl-acetic acid amide.

From the Department of Experimental Pharmacology, Madom's Laboratories, Mexico, D. F.
Received for publication Oct. 10, 1957.

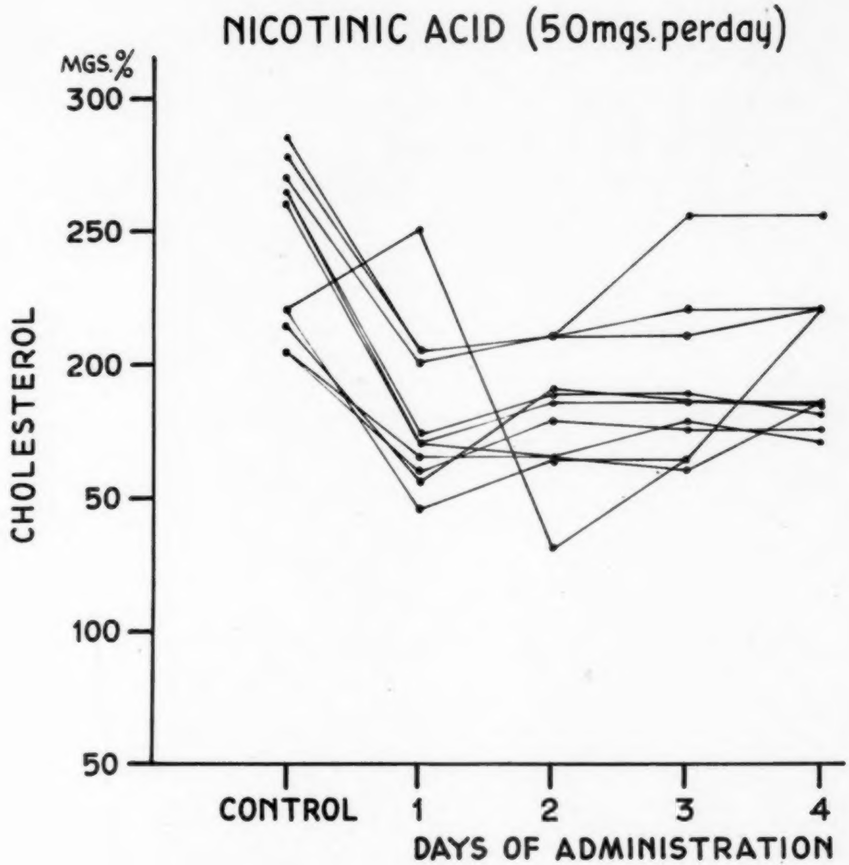

Fig. 1.—Graph plotted from Table I.

TABLE I. NICOTINIC ACID (50 MG. DAILY)

DOG	CHOLESTEROL LEVELS (MG. %) DURING PERIOD OF ADMINISTRATION					
	CONTROL	FIRST DAY	SECOND DAY	THIRD DAY	FOURTH DAY	9 DAYS LATER
1, A	205	160	178	175	175	200
1, B	220	145	163	163	220	220
1, C	215	156	190	185	183	215
1, D	278	205	210	255	255	278
2, E	265	170	185	185	185	265
2, F	285	205	210	220	220	285
2, G	270	200	210	210	220	278
2, H	220	250	130	163	163	220
3, I	205	165	165	178	170	210
3, J	260	170	165	160	185	270
3, K	265	173	188	188	180	268

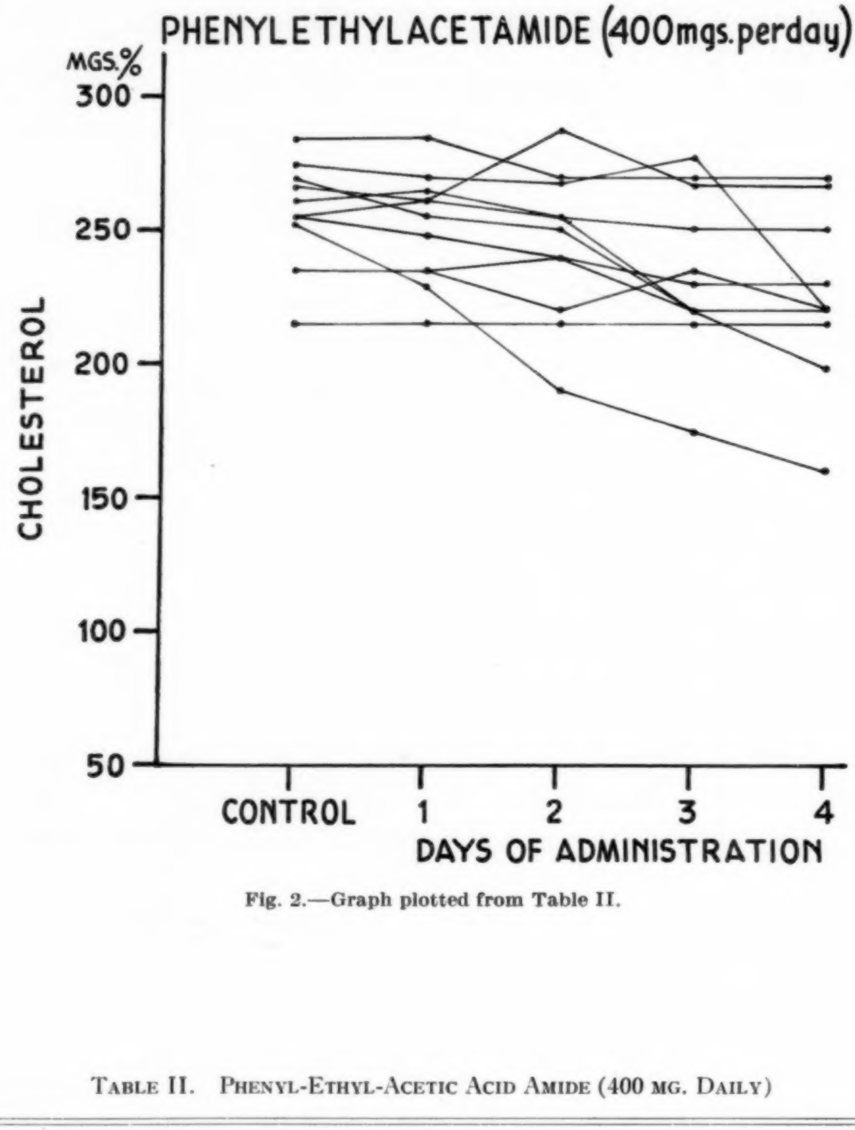

Fig. 2.—Graph plotted from Table II.

TABLE II. PHENYL-ETHYL-ACETIC ACID AMIDE (400 MG. DAILY)

DOG	CHOLESTEROL LEVELS (MG. %) DURING PERIOD OF ADMINISTRATION					
	CONTROL	FIRST DAY	SECOND DAY	THIRD DAY	FOURTH DAY	9 DAYS LATER
1, A	255	248	240	230	230	250
1, B	267	261	288	267	267	270
1, C	252	229	190	175	160	251
1, D	270	255	250	220	198	275
2, E	275	270	268	278	220	275
2, F	285	285	270	270	270	285
2, G	215	215	215	215	215	215
2, H	262	265	255	220	220	262
3, I	255	261	255	250	250	255
3, J	235	235	220	235	220	235
3, K	235	235	240	220	220	235

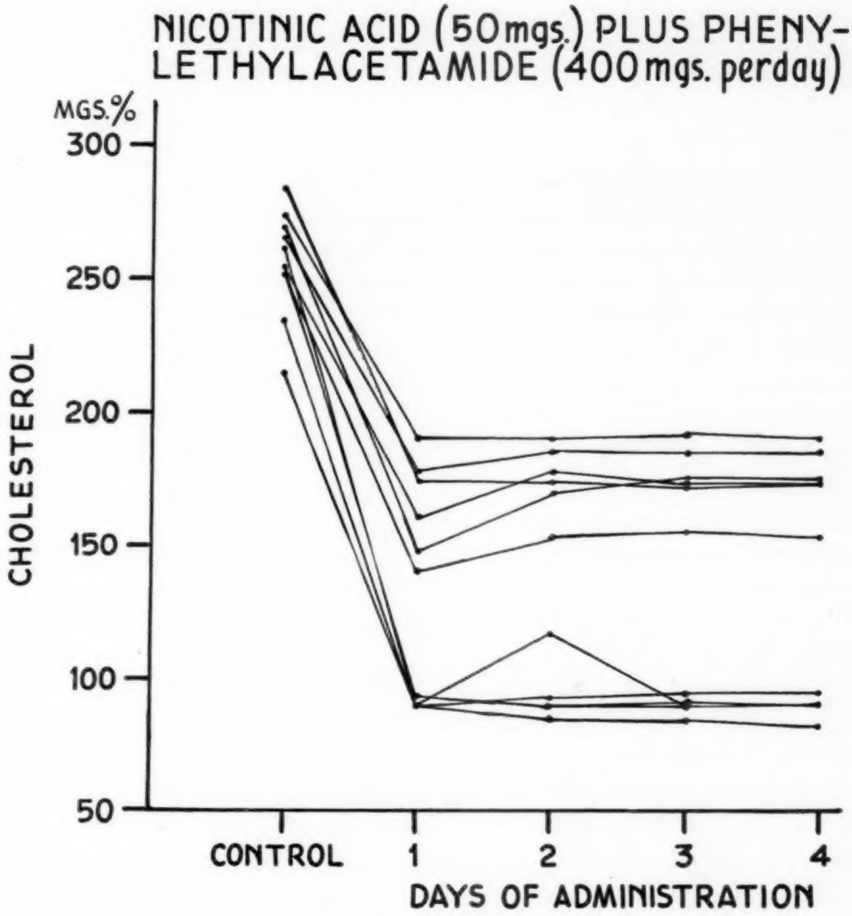

Fig. 3.—Graph plotted from Table III.

TABLE III. NICOTINIC ACID (50 MG. DAILY) PLUS PHENYL-ETHYL-ACETIC ACID AMIDE (400 MG. DAILY)

DOG	CHOLESTEROL LEVELS (MG. %) DURING PERIOD OF ADMINISTRATION					
	CONTROL	FIRST DAY	SECOND DAY	THIRD DAY	FOURTH DAY	9 DAYS LATER
1, A	255	160	178	174	174	255
1, B	267	178	185	185	185	267
1, C	252	140	153	155	153	252
1, D	270	148	170	175	175	265
2, E	275	190	190	192	190	270
2, F	285	175	175	172	175	290
2, G	215	90	118	90	90	215
2, H	262	90	85	85	82	260
3, I	255	93	90	90	91	260
3, J	235	90	93	95	95	240
3, K	235	93	90	92	90	240

We extracted 5 cm.^{3} of blood from each of the dogs every 24 hours, and the cholesterol was estimated by the Bloor method.

The results are shown in Tables I, II, and III, and in the graphs of Figs. 1, 2, and 3.

DISCUSSION

As can be appreciated from the data in the tables, the nicotinic acid in daily doses of 50 mg. lowers the cholesterol levels in the blood. We see, therefore, that the average reduction on the first day was 26 per cent and on the fourth day 21 per cent. This can be interpreted as a rapid and sustained effect of the drug, although a longer period of time is required for administration in order to judge the duration of said hypocholesterolemic effect.

The action of the phenyl-ethyl-acetic acid amide in daily doses of 400 mg. is less marked and slower. The average reduction of the cholesterol with this drug was 4 per cent during the first day, and it rose to 14 per cent on the fourth day.

The combination of 50 mg. of nicotinic acid and 400 mg. of phenyl-ethyl-acetic acid amide administered daily demonstrated a more marked and sustained hypocholesterolemic effect than did each drug administered separately. Therefore, there was an average reduction of 49 per cent during the first day, and 47 per cent on the fourth day.

It is known that the hypocholesterolemic effect of the drugs studied here is greater in subjects with a high cholesterol level than in those with a normal cholesterol level. In this first communication the study has been made on normal dogs. In our second report we will present the results obtained (1) during a more prolonged administration over a period of weeks, and (2) on a group of dogs with induced hypercholesterolemia.

SUMMARY

1. A study has been made of the action of nicotinic acid, of phenyl-ethyl-acetic acid amide, and of the combination of both substances on the cholesterol present in the blood of normal dogs during a short period of time.

2. The hypocholesterolemic effect of the nicotinic acid and the phenyl-ethyl-acetic acid amide was verified. The nicotinic acid had a more rapid and marked effect on the cholesterol level than did the phenyl-ethyl-acetic acid amide.

3. The combination of the nicotinic acid and the phenyl-ethyl-acetic acid amide had a more marked and sustained hypocholesterolemic effect than did either one of the substances separately.

4. It is considered that these preliminary results justify an investigation over longer periods of time in normal animals and in animals with an induced hypercholesterolemia, as well as in patients with different cholesterol serum levels.

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Book Reviews

HERZ-UND GEFÄSSERKRANKUNGEN. By R. Völker, Darmstadt, 1957, D. Steinkopff, 166 pages, 106 illustrations.

Over the past decade the author has developed a combination of methods which permits a more detailed diagnosis of the functional state of peripheral circulation than do the clinical routine methods, but which is simple enough to be used, in the author's words, by a "geschickte Krankenschwester" (skilled nurse). The technique includes photoelectric recording of the pulse and peripheral arterial O_2 saturation from the finger cup; continuous recording of CO_2 and O_2 content of the expired air, together with respiratory volume, by means of an instrument manufactured by Hartmann and Braun; and continuous recording of skin temperature. These methods are used in resting condition, in response to thermal stimuli, and under physiologic stress situations, particularly in hypoxia produced by rebreathing or by breathing a 10 per cent O_2/N_2 mixture. The compact pickup for recording of peripheral circulation and O_2 saturation, strapped on the middle finger (Fig. 106), is in some respects an improvement of Matthes' method. Of these methods, by far the largest space is devoted to the photoelectric recording of the digital volume pulse (pp. 3-119). Deformation of the contour was found not only in peripheral vascular disease, but also in cardiac diseases and conditions such as coronary insufficiency and myocardial infarction, decompensation, mitral and aortic valvular defects, auricular fibrillation, etc. In regard to the variety of cardiocirculatory pathology investigated, this is one of the most comprehensive applications of photoelectric plethysmography. The author's view that any type of cardiac pathology involves also the peripheral circulation is, perhaps, not new, but the detailed objective demonstration of this functional relationship fills an important gap. While for the functional capacities of a cardiac patient the state of peripheral circulation is undoubtedly important, there is a tendency to some exaggeration. Since impairment of peripheral circulation was found in patients with definite coronary artery disease, the author considers an abnormal pulse tracing in dubious angina pectoris (with normal ECG) as positive evidence for coronary insufficiency. However, the deformation of the pulse contour, reaction to thermal stimuli, etc., does not appear to be specific for any cardiac condition, and in the absence of statistical evaluation of normal distribution, of incidence of peripheral involvement in cardiac patients, and of correlation between peripheral and cardiac involvement, such diagnostic implication appears to be premature.

As a whole, however, the experience of the author is encouraging and his methods promise to be a valuable supplement to the present clinical routine examination.

E. S.

CARDIO-CHARTING. Universal Method of Recording Heart Auscultation. By Arthur Briskier, M.D., New York, 1957, The Macmillan Company.

The ability to observe accurately and to describe clearly is a skill which every student of medicine must develop. His task is made more difficult than it need be by the various terms used by different authors and teachers to indicate abnormalities in the quality, intensity, and timing of the heart sounds and murmurs.

In this monograph the author aims to increase interest in careful cardiac auscultation and to introduce an internationally acceptable system for recording the findings graphically. The method is a modification of one in common use, whereby a diagram is made to resemble what one believes the phonocardiogram would show. The colors blue and red are used to represent sounds

and murmurs, respectively, and a number of symbols, some borrowed from standard musical notation, is included. The bulk of the text consists of illustrations of the findings in various heart diseases.

Amplitude in the phonocardiogram is related to sound intensity, whereas the author uses the amplitude of his symbols for heart sounds to represent pitch variations; he indicates intensity by the musical notation: pp,ff & c. Statements such as "A calcified and narrowed aorta (Medial arterial Monckeberg's sclerosis) produces a loud, harsh, mid-diastolic murmur." (p.26), or the illustration of presystolic accentuation to the diastolic murmur of mitral stenosis in the presence of atrial fibrillation (p.39) may confuse the undergraduate student.

The book may be of interest to those who teach physical diagnosis and who are concerned with diseases of the heart.

D. S.

DIGITALIS. Edited by E. Grey Dimond, M.D., Springfield, Ill., 1957, Charles C Thomas, Publisher, 255 pages.

In this volume are published the lectures given by several speakers at a two-day postgraduate program devoted entirely to digitalis at the University of Kansas Medical School, in February, 1956. The book has been carefully edited so that, unlike many published lectures, it reads smoothly and there is no repetition.

Investigators who have devoted many years of research to digitalis, such as Chen, Bing, Batterman, Lown, Luisada, and Friedman, are contributors to this volume. The major fields of research are covered. Of special interest are reports on research which indicate the mechanism of action. It appears quite clear now that digitalis improves the efficiency of the failing heart without increasing the oxygen consumption, possibly by a direct action on contractile proteins. The relationship of digitalis to electrolyte distribution, particularly of potassium and sodium, is discussed in considerable detail.

The last chapter records a panel discussion participated in by the various speakers.

An excellent index makes this book a good reference work on digitalis.

A. D.

DIE CHIRURGIE DES HERZENS UND DER GROSSEN GEFÄSSE. By Professor Frey and Dr. Kuetgens, of the University of Munich.

The authors have compiled a treatise which covers, as the subtitle in translation states, "Anatomy, Physiology, Embryology, Pathology, Pathologic Physiology, Clinical Medicine, Diagnosis and Operative Treatment."

To accomplish this in 387 pages of text, with 244 illustrations, is a task which surprises the reader more by its near success than its failure.

The printing is at a level seldom equalled in this country and the illustrations are of a high order. The material is well organized with, incidentally, a table of contents more useful than the index. Emphasized especially are those valvular lesions and congenital anomalies presently recognized as amenable to surgical correction, and the surgery of coronary disease. Also included are sections on wounds of the heart, lung embolus, and lesions of the pericardium. Each chapter follows a logical order of presentation which makes the text a convenient reference work. The well-established knowledge concerning the heart and its functioning is set forth succinctly but in considerable detail. In areas where opinions vary there are a large number of references to the literature, a surprising amount of which is in the English language, particularly that pertaining to surgical techniques and clinical research. This perhaps points out in what respect this volume will be most useful in Germany, where only recently is cardiac surgery catching up to the remarkable advances which have been largely pioneered in the United States and in England. In this dynamic field no book can hope to keep up. This text does, however, maintain a com-

mendable perspective in the midst of the tremendous amount of material available up until February, 1956. Not least in this book's attractions are the historical resumés included in nearly every section.

N. M. S.

Clinical Laboratory Diagnosis. By Samuel A. Levinson and R. P. McFate, Ed. 5, Philadelphia, 1956, Lea & Febiger, 1246 pages, 244 illustrations. Price $12.50.

The fifth edition of this text presents a number of changes. The chapters on hematology and bacteriology have been completely rewritten, while the text in other sections has been rearranged, revised, and brought up to date. The inclusion of micro chemical methods is a valuable addition. These changes add some 100 pages to the size of the book.

Although the authors' stated objective is to present to the medical student, intern, the resident physician, and the practising physician, as well as the medical technologist, a suitable review of clinical laboratory diagnosis sufficient to meet their general needs, the text and description of methods is perhaps too detailed for the general reader. On the other hand, although the scope of the book is wide, the authors' choice of their preferred technique does not offer to the specialist the opportunity of selecting a method which may be more suitable for his particular needs.

Nevertheless, this text is a valuable reference volume in the field of clinical laboratory diagnosis. It will find its most suitable location on the reference shelves of the medical library or the clinical laboratory.

K. R. M.

Announcements

A Continuation Course in Internal Medicine for Specialists will be presented from March 17 to 19, 1958, at the Center for Continuation Study on the campus of the University of Minnesota.

The guest faculty will include Dr. Stewart Wolf, Professor and Chairman, Department of Medicine, University of Oklahoma School of Medicine, Oklahoma City, and Dr. Paul Wood, Institute of Cardiology, London, England, who will also deliver the George E. Fahr Lecture on Tuesday, March 18. The remainder of the faculty will include members of the faculties of the University of Minnesota Medical School and the Mayo Foundation. The course will be presented under the direction of Dr. N. L. Gault, Jr., Director, Department of Continuation Medical Education.

Lodging and meal accommodations are available at the Center for Continuation Study.

The International Society of Cardiology Foundation was established in Chicago, in January, 1957, for the purpose of supporting research in the cardiovascular field anywhere in the world. Requests for such support can be sent to the Board of Directors or to the Advisory Committee of the Foundation, as listed below, or to the office of the Foundation in Chicago, c/o Dr. Louis Katz, Michael Reese Hospital. A member receiving such application will forward the information to the President, Dr. Paul D. White, who will then pass the recommendation on for processing to other members of the Advisory Committee. The recommendations of the Committee transmitted to the Board of Directors will permit the latter to act.

The Foundation is in a position to receive funds from any part of the world for the purpose for which it was established. In its beginning the Foundation's available funds are quite limited but it is expected that they will increase with the knowledge that such a source of support of international cardiovascular research exists.

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